Association of FTO Polymorphisms with Obesity and Obesity-Related Outcomes in Portuguese Children

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Abstract

Background: Several studies have reported an association between single nucleotide polymorphisms in the first intron of the FTO gene and body mass index (BMI) or obesity. However, this association has not yet been studied among the Portuguese population. This study aims to assess the association of three FTO polymorphisms (rs1861868, rs1421085 and rs9939609) with obesity-related outcomes in a sample of Portuguese children.

Methods: We examined a total of 730 children, 256 normal-weight (55.9% girls), 320 overweight (45.3% girls) and 154 obese (53.2% girls), aging from 6 to 12-years-old, recruited randomly from public schools in the central region of Portugal. DNA samples were genotyped for the three polymorphisms by allelic discrimination TaqMan assay. Association of the FTO polymorphisms with several anthropometric traits was investigated. Additionally, we tested association with the risk of obesity using overweight and obese vs. normal-weight children.

Results: We found significant associations of rs9939609 and rs1421085 polymorphisms with weight, BMI, BMI Z-score, waist circumference and hip circumference, even after age and gender adjustment (p<0.05 in all traits). For rs1861868 polymorphism, marginally significant associations were obtained with weight (p=0.081) and BMI (p=0.096) after adjustment for age and gender. In case-control studies, both rs9939609 and rs1421085 polymorphisms were significantly associated with obesity (OR 1.97; 95% CI, 1.08–3.59; p=0.026; OR 2.11; 95% CI, 1.17–3.81; p=0.013, respectively) but not with overweight (p>0.05). Haplotype analyses identified two combinations (ACA and GCA) associated with a higher risk of obesity (OR 1.53; 95% CI, 1.06–2.22; p=0.023; OR 1.73; 95% CI, 1.06–2.87; p=0.030, respectively).

Conclusions: This study provides the first evidence for the association of FTO polymorphisms with anthropometric traits and risk of obesity in Portuguese children.

Introduction

Overweight and obesity are a major health issue associated with risk factors for the development of hypertension, type 2 diabetes and cardiovascular diseases [1]. This complex phenotype results from the interaction of environmental and multiple genetic factors influencing body mass index (BMI), with heritability estimated at 40–70% [2].

The advent of Genome Wide Association Studies (GWAS) emerged as a powerful approach to identify genetic variants associated with common diseases [3]. Until now, GWAS deliver the identification of at least 52 genetic loci robustly associated with obesity [4]. In 2007, a strong association was detected between common single nucleotide polymorphisms (SNPs) in the first intron of the fat mass and obesity-associated gene (FTO), on the chromosome 16q12.2, and risk of obesity [5,6]. Of those SNPs, the rs9939609 is one of the most extensively studied, explaining about 1% of BMI heritability [5]. Each rs9939609-A allele in this gene increases body weight by 1.5 kg in adult, with similar effects observed in children and adolescents [5]. Subsequently, several other studies have consistently confirmed the association of a cluster of SNPs within the first intron of the FTO gene with obesity-related traits in several European [5–10], Asian [11–15] and African [16,17] populations.

Knowledge of the genetic risk factors associated with common childhood obesity, can be helpful to design prevention strategies. Although in the Portuguese population several studies were made concerning the prevalence of overweight and obesity [18,19], until now, no studies reporting the association of genetic variants with the risk of common obesity have been generated. Thus, the aim of this study was to evaluate the association between three FTO SNPs, including rs9939609 and rs1421085, prominent in the literature, and rs1861868, yet poorly studied, with the susceptibility to obesity in a sample of Portuguese children.
Materials and Methods

Study subjects

Children aging 6 to 12 years old were randomly selected from several public schools in the central region of Portugal. A total of 1433 Portuguese children of European descent comprising 747 girls and 686 boys were recruited [18], and were classified using age and sex specific BMI cut-offs provided by the International Obesity Task Force (IOTF) [20]. From the 1433 analysed children, three BMI groups were formed: 320 subjects were classified as overweight (resulting from the BMI in adult’s cutpoints between $ \geq 25$ kg/m$^2$ and $< 30$ kg/m$^2$), 154 as obese (BMI $ \geq 30$ kg/m$^2$), and 959 as normal weight (BMI $< 25$ kg/m$^2$).

The study protocol was approved by Direcção Geral de Inovação e de Desenvolvimento Curricular, the ethical Committee of the Portuguese Ministry of Education, and was conducted in accordance with the institutional guidelines of the University of Coimbra. Written informed consent was previously obtained from the children’s parents.

Anthropometric Measurements

Height (cm) and weight (kg) were taken with participants dressed in lightweight clothing without shoes. Waist circumference (cm) was measured midway between the lowest rib and the iliac crest, to the nearest 0.1 cm after inhalation and exhalation. Hip circumference (cm) was measured at the point over the buttocks yielding the maximum circumference. The BMI was calculated with the weight in kilograms divided by the square of height in meters (kg/m$^2$). Abdominal obesity was defined using the sex and age-specific $ \geq 90^{th}$ waist circumference percentile [21].

Selected and genotyping of the FTO polymorphisms

Samples were analysed for three SNPs located within first intron of the FTO gene: two that have been closely associated with obesity and prominent in the literature, rs9939609 (position: chr16:53790402), described by Frayling et al. [5], and rs1421085 (position: chr16:53800954), reported in the work of Dina et al. [7], and the yet poorly studied rs1861868 polymorphism (position: chr16:53790402), described in two studies [8,9].

A buccal swab sample was collected from each child for genetic studies. The genomic DNA was extracted from buccal cells using the PureLink Pro 96 Genomic DNA Kit (Invitrogen Corporation, Carlsbad, CA, USA), according to the instructions of the manufacturer, and was only used for the SNPs genotyping.

Samples were genotyped for the three FTO SNPs by allelic discrimination assays using TaqMan probes (C_30090620_10, C_11717119_10 and C_8917103_10; Applied Biosystems, Foster City, USA). Fluorescence was visualized through a MiniOpticon real-time PCR system (Bio-Rad, Hercules, CA, USA).

To assess genotyping reproducibility, a selection of 10% random samples was re-genotyped for all SNPs with 100% concordance by the Single Strand Conformation Polymorphism (SSCP) method or sequencing by the Sanger’s dideoxy chain discrimination assays using TaqMan probes (C_30090620_10, C_11717119_10 and C_8917103_10; Applied Biosystems, Foster City, USA), Fluorescence was visualized through a MiniOpticon real-time PCR system (Bio-Rad, Hercules, CA, USA).

We performed association analysis under the additive model using BMI case-control groups (Table 3). When compared obese vs. normal-weight groups the rs9939609 AA genotype showed significant association with risk of obesity (OR 1.97; 95% CI, 1.08–3.59; p = 0.026), but not the AT genotype (OR 1.47; 95% CI, 0.91–2.38; p = 0.116). Accordingly, 23.4% of the obese individuals were AA homozygotes compared to 16.2% of the control subjects.
Association was also observed with increased risk of obesity for the rs1421085 CC genotype (OR 2.11; 95% CI, 1.17–3.81; \( p = 0.013 \)), but not for the CT genotype (OR 1.48; 95% CI, 0.90–2.43; \( p = 0.123 \)). For this SNP, 26.6% of the obese individuals had the CC genotype, against 17.7% with normal weight. For the rs1861868 SNP, it was not found a significant association with obesity (OR 1.55; 95% CI, 0.74–2.47; \( p = 0.332 \)) (Table 3). Association analysis under an allelic model, comparing obese vs. normal-weight groups, showed similar significant results for rs9939609 (OR 1.44; 95% CI, 1.08–1.91; \( p = 0.012 \)) and rs1421085 (OR 1.48; 95% CI, 1.12–1.98; \( p = 0.007 \)), but not for rs1861868 (OR 1.20; 95% CI, 0.89–1.61; \( p = 0.228 \)). We detected no significant association when comparing overweight vs. normal-weight groups (\( p = 0.05 \)) (Table 3).

Haplotype analysis associating the three studied FTO SNPs (rs1861868-rs1421085-rs9939609), revealed all the eight possible haplotypes, being the most commons GTT (33%), GCA (32%), ATT (19%) and GCA (12%) (Table 4). Three haplotypes had an estimated frequency below 1% (GCT, ATA and GTA). Compared with the most common and non-risk haplotype (GTT), two haplotypes (GCA and GCA) were significantly associated with a higher risk of being obese (OR 1.534; 95% CI, 1.06-2.22; \( p = 0.023 \); OR 1.739; 95% CI, 1.06-2.87; \( p = 0.030 \), respectively).

Regarding allelic combinations, SNPs rs9939609 (position: chr16:53820527) and rs1421085 (position: chr16:53800954), distant from one another about 19.6 kb, were found in high LD (\( D' = 0.91; \ r^2 = 0.82 \)). The rs1861868 SNP (position: chr16:53790402) was found in low LD (\( D' = 0.39; \ r^2 = 0.11 \)) with rs9939609, distant about 30.1 kb, as well with rs1421085 (\( D' = 0.44; r^2 = 0.13 \)), distant about 10.6 kb.

### Discussion

Recently, the growth in studies regarding the association of obesity, or obesity-related traits, with SNPs in the FTO gene has been reported for several populations across the world [5–17]. Most studies confirmed that FTO SNPs are strongly associated with BMI and/or obesity [5–17]. However, in Portugal there are no studies to confirm the association between genetic variants and common obesity, which could permit the comparison with data from other European populations. Despite the similar genetic background between European populations, it is known that for several polymorphisms, frequencies can vary within different Caucasian populations [29,24]. Moreover, a few studies failed to associate some FTO polymorphisms and obesity [25,26], highlighting the need of more studies in different populations to better understand the role of FTO gene in obesity. The present study is the first to test whether common FTO gene SNPs are associated with obesity or to related anthropometric traits in children of Portuguese origin.

Our research showed a significant genetic association of rs9939609 and rs1421085 SNPs, in strong linkage disequilibrium (\( r^2 = 0.82 \)), with the risk of obesity in Portuguese children. Consistently, we also observed significant association with several anthropometric measurements including weight, BMI, WC and HC. These results are similar to those found in previous studies performed in other European populations reporting the association of FTO SNPs with obesity [5–7,27]. In our study, the effect obtained for each copy of rs9939609-A allele was \(-0.6 \text{ kg/m}^2\) in BMI, \(-1.2 \text{ cm} \) in WC and \(-1.7 \text{ kg} \) in weight, similar to the effect stated by Frayling et al. [5].

Regarding rs1861868 SNP, association with BMI was first described in a sample of Old Order Amish with low physical activity [8] and replicated in a sample of Spanish children [9]. However, in this last study, it was not found a significant association with BMI or obesity. Our study showed an association with weight, BMI, WC and HC, with marginally significant results for weight (\( p = 0.081 \)) and BMI (\( p = 0.096 \)) after adjusting for age and gender. This suggests that stronger statistically significant results could be obtained by increasing the sample size.

Our results show that in Portuguese children the rs9939609 and rs1421085 SNPs are in association with obesity, with no differences between girls and boys, and in line with previously reported studies in other European populations [5–10]. We found an OR of 1.44 for the rs9939609 SNP under an allelic model. This result appears similar to the effects reported by Frayling et al [5] in UK children (OR = 1.35; 95% CI, 1.14–1.61), and Hinney et al. [28] in German children/adolescents (OR = 1.57; 95% CI, 1.30–1.90). We also found an OR of 1.48 for the rs1421085 SNP similar to that reported by Dina et al. [7] in French children (OR = 1.43; 95% CI, 1.25–1.64), and Meyre et al. [29] in German children (OR = 1.50; 95% CI, 1.25–1.79). The rs9939609 was the most replicated SNP associated with obesity across the world, nevertheless, in our study the strongest association was obtained with the rs1421085 SNP (OR 2.11; 95% CI, 1.17–3.81; \( p = 0.013 \), additive model), similar to the result obtained by Price et al. [30] in a sample of Caucasian women when analysing both SNPs.

None of the three study SNPs showed evidence of association with overweight in the sample. This means that the FTO risk allele predominates in individuals with higher BMI; hence the association was detected in severe obesity rather than in overweight population, similarly to the results obtained by Liu et al. [14].

The FTO risk allele frequencies observed in our study are within range of reported values in European populations [5–10]. Both rs9939609 and rs1421085 SNPs were found in high LD (\( r^2 = 0.82 \)) in our study reflecting the high LD across the 19.6 kb region within the intron 1 of FTO gene. Polymorphisms rs9939609 and rs1421085 are both part of a set of FTO-associated SNPs within a 47 kb LD block encompassing parts of the first two introns as well as exon 2 of the FTO gene [31] suggesting that they all tag a same genetic signal in that region. The low LD (\( r^2 = 0.13 \)) observed in

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### Table 1. General characteristic of the sampled children by phenotype distribution.

| Characteristics | Overall | Obesity | Overweight | Normal |
|-----------------|---------|---------|------------|--------|
| N               | 730     | 256     | 320        | 154    |
| Girls (%)       | 50.7    | 55.9    | 45.3       | 53.2   |
| Age (years)     | 9.1 ± 1.7 | 8.6 ± 1.6 | 9.5 ± 1.6 | 9.0 ± 1.7 |
| Height (cm)     | 136.2 ± 11.7 | 131.1 ± 11.1 | 139.5 ± 11.1 | 137.9 ± 10.6 |
| Weight (kg)     | 37.2 ± 11.3 | 28.1 ± 6.6 | 40.2 ± 9.3 | 46.1 ± 11.0 |
| BMI (kg/m²)     | 19.6 ± 3.4 | 16.1 ± 1.5 | 20.3 ± 1.8 | 23.8 ± 2.5 |
| BMI Z-score     | 0.93 ± 0.97 | -0.15 ± 0.78 | 1.3 ± 0.23 | 1.99 ± 0.23 |
| Waist circumference (cm) | 67.2 ± 7.8 | 60.3 ± 4.5 | 68.9 ± 5.4 | 75.1 ± 6.6 |
| Hip circumference (cm) | 79.0 ± 10.3 | 70.4 ± 6.5 | 81.9 ± 8.0 | 87.1 ± 9.4 |
| WHR             | 0.85 ± 0.06 | 0.86 ± 0.06 | 0.85 ± 0.06 | 0.87 ± 0.05 |

Data are presented as mean ± standard deviation.

*Phenotype distribution was determined using age and gender specific BMI cut-offs provided by the International Obesity Task Force (IOTF).

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Table 2. Comparison of anthropometric parameters among different genotypes of the FTO rs9939609, rs1421085 and rs1861868 polymorphisms in the sampled Portuguese children.

| Characteristics | rs9939609 | rs1421085 | rs1861868 | |
|-----------------|-----------|-----------|-----------|---|
|                  | TT        | AT        | AA        | TT  | CT  | CC  |
| N (%)            | (220)     | (357)     | (144)     | (213) | (368) | (146) |
|                  | (30.5)    | (49.5)    | (20.0)    | (29.3) | (50.6) | (20.1) |
| Height (cm)      | 134.7±    | 136.8±    | 137.6±    | 134.8± | 136.5± | 137.4± |
|                  | 12.2      | 11.5      | 11.0      | 12.1  | 11.7  | 10.6  |
|                  | 0.031     | 0.044     | 0.090     | 0.077 |
| Weight (kg)      | 35.5±     | 37.8±     | 38.9±     | 35.6± | 37.4± | 38.7± |
|                  | 11.7      | 11.1      | 11.1      | 11.8  | 11.2  | 10.9  |
|                  | 0.010     | 0.019     | 0.031     | 0.032 |
| BMI (kg/m²)      | 19.0±     | 19.7±     | 20.2±     | 19.1± | 19.6± | 20.2± |
|                  | 3.4       | 3.4       | 3.5       | 3.5   | 3.5   | 3.5   |
|                  | 0.005     | 0.018     | 0.010     | 0.022 |
| BMI Z-score      | 0.77±     | 0.98±     | 1.09±     | 0.76± | 0.96± | 1.09± |
|                  | 1.05      | 0.93      | 0.91      | 1.1   | 0.91  | 0.9   |
|                  | 0.006     | 0.011     | 0.005     | 0.009 |
| WC (cm)          | 66.0±     | 67.7±     | 68.4±     | 66.0± | 67.5± | 68.5± |
|                  | 7.9       | 7.6       | 7.7       | 7.6   | 7.6   | 7.8   |
|                  | 0.005     | 0.016     | 0.007     | 0.013 |
| HC (cm)          | 77.4±     | 79.6±     | 80.5±     | 77.6± | 79.3± | 80.4± |
|                  | 10.5      | 10.0      | 9.0       | 10.6  | 10.1  | 9.8   |
|                  | 0.008     | 0.017     | 0.030     | 0.035 |
| WHR              | 0.86±     | 0.85±     | 0.85±     | 0.85± | 0.85± | 0.86± |
|                  | 0.03      | 0.06      | 0.05      | 0.06  | 0.05  | 0.05  |
|                  | 0.096     | 0.966     | 0.966     | 0.986 | 0.799 |
|                  | 0.86      | 0.85      | 0.85      | 0.85  | 0.85  | 0.85  |
|                  | 0.05      | 0.05      | 0.05      | 0.05  | 0.05  | 0.06  |
| Abbreviations: BMI, body mass index; BMI Z-score, body mass index standard deviation score; WC, waist circumference; HC, hip circumference; WHR, waist-to-hip ratio. 
 p-values were analyzed by one-way ANOVA. 
 p²-values were adjusted for age and gender. p-value significant (p<0.05) in bold. 
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and rs1421085 have increased risk of obesity. haplotypes combining the risk alleles for the two SNPs rs9939609 (haplotype ACT, presenting only one risk allele, no association alleles A and C for rs9939609 and rs1421085, respectively. For the ACA (two common haplotypes that seem to confer risk to obesity were decline between these two SNPs. As we show (Table 4) the only the studied obesity related parameters, suggesting that LD block complement the lower genetic predictive power of rs1861868 for our study between rs1861868 5 9

In 1962, Neel proposed the thrifty gene hypothesis [32]

Our study between rs1861868 5’ apart 10.6 kb from rs1421085, complement the lower genetic predictive power of rs1861868 for the studied obesity related parameters, suggesting that LD block decline between these two SNPs. As we show (Table 4) the only two common haplotypes that seem to confer risk to obesity were ACA (p = 0.023) and GCA (p = 0.030), which include both risk alleles A and C for rs9939609 and rs1421085, respectively. For the haplotype ACT, presenting only one risk allele, no association (p = 0.209) with obesity was found. This seems to reflect that haplotypes combining the risk alleles for the two SNPs rs9939609 and rs1421085 have increased risk of obesity.

In 1962, Neel proposed the thrifty gene hypothesis [32] suggesting that populations whose ancestral environments were characterized by periods of feast and famine, experienced positive selection for thrifty alleles that promote the storage of fat and energy. Thus, under modern conditions, populations with such thrifty alleles are expected to have high rates of obesity. Regarding the ancestral alleles for SNPs rs9939609 and rs1421085 comparing sequence similarity with non-human primates, the ancestral rs9939609-A allele is associated with the obesity risk but not the ancestral rs1421085-T allele. This different genetic association pattern is not consistent with the thrifty gene hypothesis, as also suggested in a previous report [33], because under this hypothesis we should expect a similar pattern regarding ancestry of the risk alleles.

In conclusion, this is the first study reporting allele and genotype frequencies of the FTO polymorphisms in the Portuguese population. We found evidence that the previously reported common polymorphisms rs9939609 and rs1421085 in FTO gene increase the risk of obesity in the Portuguese children. Further studies on other polymorphisms from FTO and other genes are needed, to establish the genetic basis contributing to the risk of obesity in the Portuguese population.

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Author Contributions

Conceived and designed the experiments: CN LM. Performed the experiments: DA. Analyzed the data: DA CN LM. Contributed reagents/materials/analysis tools: CN LM. Wrote the paper: DA CN LM.

References

1. Hetherington MM, Cecil JE (2010) Gene-environment interactions in obesity. Forum Nutr 63: 195–203.
2. Paquot N, De Fines J, Rorive M (2012) Obesity: a model of complex interactions between genetics and environment. Rev Med Liege 67(5–6): 332–336.

3. Yeo GS (2011) From GWAS to biology: lessons from FTO. Ann N Y Acad Sci 1229: 162–171.

4. Loos R (2012) Genetic determinants of common obesity and their value in Prediction. Best Pract Res Clin Endocrinol Metab 26: 211–226.

5. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, et al. (2007) A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 316(5826): 889–894.

6. Scuteri A, Sanna S, Chen WM, Uda M, Albai G, et al. (2007) Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. PLoS Genet 3(7): 1200–1210.

7. Dina C, Meyre D, Gallina S, Durand E, Körner A, et al. (2007) Variation in the FTO gene is associated with obesity and modulates BMI in the Chinese population. J Hum Genet 52: 1031–1035.

8. Rampersaud E, Mitchell B, Pollin T, Fu M, Shen H, et al. (2008) Physical activity and the association of common FTO gene variants with body mass index and obesity. Arch Inter Med 168(16): 1791–1797.

9. Rodríguez-López R, González-Carpio M, Serrano MV, Torres G, García de Cáceres MT, et al. (2010) Association of FTO gene polymorphisms and morbid obesity in the population of Extremadura. Endocrinol Nitr 57(5): 203–209.

10. Zavattari P, Loche A, Pillai S, Ihba A, Mois L, et al. (2011) rs9939609 in the FTO gene is associated with obesity but not with several biochemical parameters in Sardinian obese children. Ann Hum Genet 75: 648–654.

11. Chang YC, Liu PH, Lee WJ, Chang TJ, Jiang YD, et al. (2010) Association of FTO gene with obesity in children of Caucasian and African American ancestry reveals a common tagging SNP. PLoS ONE 5: e1746.

12. Song Y, You NC, Hsu YH, Howard BV, Launer LD, et al. (2008) FTO Polymorphisms are associated with obesity but not diabetes risk in postmenopausal women. Obesity 16(11): 2472–2480.

13. Fang H, Li Y, Du S, Hu X, Zhang Q, et al. (2010) Variant rs9939609 in the FTO gene is associated with body mass index among Chinese children. BMC Med Genet 11: e136.

14. Liu Y, Liu Z, Song Y, Zhou D, Zhang D, et al. (2010) Meta-analysis added power to identify variants in FTO associated with type 2 diabetes and obesity in the Asian population. Obesity 18(8): 1619–1624.

15. Macková S, Bernasovský I, Gabržeková D, Bőžíková A, Bernasovský J, et al. (2012) Association of the FTO rs9939609 polymorphism with obesity in Roma/Gypsy population. Am J Phys Anthropol 147(1): 30–34.

16. Grant SFA, Li M, Bradfield JP, Kim CE, Annaiah K, et al. (2008) Association analysis of the FTO gene with obesity in children of Caucasian and African ancestry reveals a common tagging SNP. PLoS ONE 3: e1746.

17. Song Y, You NC, Hsu YH, Howard BV, Launer RD, et al. (2008) FTO Polymorphisms are associated with obesity but not diabetes risk in postmenopausal women. Obesity 16(11): 2472–2480.

18. Albuquerque D, Nobrega C, Samouda H, Manco L (2012) Assessment of obesity and abdominal obesity among Portuguese children. Acta Med Port 25(3): 167–171.

19. Padez C, Fernandez T, Mourio I, Moreira P, Rosado V (2004) Prevalence of overweight and obesity in 7-9-year-old Portuguese children: Trends in body mass index from 1970. Am J Hum Biol 16: 670–678.

20. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH (2000) Establishing a standard definition for child overweight and obesity worldwide: international survey. Br Med J 320: 1–4.

21. Cook S, Weirnman M, Auninger P, Nguyen M, Dietz WH (2003) Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988–1994. Arch Pediatr Adolesc Med 157: 821–827.

22. Excoffier L, Schneider S (2005) Arlequin ver. 3.11: An integrated software package for population genetics data analysis. Evol Bioinf Online 1: 47–50.

23. Brosagliere T, Sabeti PC, Patterson N, Vanderploeg T, Schaffner SF, et al. (2004) Genetic signatures of strong recent positive selection at the lactase gene. Am J Hum Genet 74(6): 1111–1120.

24. Weber WW (1999) Populations and genetic polymorphisms. Mol Diagn 4(4): 299–307.

25. González JR, González-Carpio M, Hernández-Sáez R, Serrano Vargas V, Torres Hitaglo G, et al. (2012) FTO risk haplotype among early onset and severe obesity cases in a population of western Spain. Obesity (Silver Spring) 20(4): 909–915.

26. Karms R, Vialli S, Tuiterle J, Sun G, Chang H, et al. (2011) Common variants in FTO are not significantly associated with obesity-related phenotypes among Samoans of Polynesia. Ann Hum Genet 75(1): 17–24.

27. Freathy RM, Timpson NJ, Lavadour DA, Pousta A, Ben-Shlomo Y, et al. (2008) Common variation in the FTO gene alters diabetes-related metabolic traits to the extent expected given its effects on BMI. Diabetes 57: 1419–1426.

28. Hinney A, Nguyen TT, Schrag A, Friedel S, Bronner G, et al. (2007) Genome-wide association (GWA) study for early onset extreme obesity supports the role of fat mass and obesity associated gene (FTO) variants. PLoS ONE 2: e1361.

29. Meyre D, Delplanque J, Chevret JC, Lecoeur C, Lobbezoo S, et al. (2009) Genome-wide association study for early-onset and morbid adult obesity identifies three new loci in European populations. Nat Genet 41: 157–59.

30. Price A, Li WD, Zhao H (2008) FTO gene SNPs associated with extreme obesity in cases, controls and extremely discordant sister pairs. BMC Medical Genetics 9: 1.

31. Fawcett KA, Barroso I (2010) The genetics of obesity: FTO leads the way. Trends Genet 26(6): 266–274.

32. Noell JV (1962) Diabetes mellitus: a “thrifty” genotype rendered detrimental by “progress”. Bulletin of the WHO 27(6): 694–703.

33. Ohashi J, Naka I, Kimura R, Natsuhara K, Yamauchi T, et al. (2007) FTO Is Associated with Obesity in Portugal.