Frequency study of the FTO and ADRB3 genotypes in a Romanian cohort of obese children

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Abstract

The human population worldwide has showed during the past years an alarming increase in the incidence of obesity in all races, sexes, social, cultural, religious or geographic environments. Romanian population has adopted generally the Western countries’ lifestyle and presently is one of the leader countries in the high incidence in obesity, especially in childhood obesity.

This study is a first approach of genotyping in a selected Romanian cohort comprising adults and children for two genes related both to energy accumulation and expenditure, respectively: FTO rs9939609 and ADRB3 rs4994. The results showed that although statistically significant in both groups, the FTO allele A was more associated with obesity in adults than in children. The FTO rs9939609 polymorphism is a common SNP in our Romanian study group, its mutant A allele showing a higher frequency than the worldwide rates. The selected ADRB3 polymorphism is a rare genetic variant in our Romanian cohort: its C allele has shown correlations, although not statistical, with obesity susceptibility, all of the heterozygous (TC) individuals belonging to obese groups, while no homozygous mutant (CC) subjects were reported. Although rare, the ADRB3 mutant frequency was higher in our Romanian groups than in the reported worldwide population. In contrast with the FTO genotype, the ADRB3 genotyping showed a higher association with the predisposition for obesity in children than in adults in our cohort.

Keywords: obesity, FTO, ADRB3, rs9939609, rs4994, allele frequencies, genetic predisposition

1. Introduction

Obesity is commonly known as the result of an unbalance between intake and expenditure, a complex multifactorial disorder involving all metabolic pathways (lipid metabolism, glucose metabolism, protein and energy metabolism, vitamin metabolism) (1, 2), in which fat mass accumulation and low energy consumption are key predisposing and etiopathogenetic factors.
Since the discovery of the Fat Mass and Obesity associated (FTO) gene in 2007 (3, 4) as the first gene ever described as being correlated with the predisposition for the common polygenic obesity, genome wide association studies (GWAS) identified a number of more than 60 chromosome regions and over 240 single nucleotide polymorphisms (SNPs) linked with the complex matrix of molecular processes involved in the pathogenesis of this complex disorder (5-9).

The common rs9939609 SNP from intron 1 of the FTO gene is the most widely correlated genetic variant with the predisposition for obesity, being involved in the fat mass accumulation process and in the hunger-satiety pathway (10-12). As a response to the FTO adiposity action, the ADRB3 gene is engaged in the energetic balance of the organism, its rather rare rs9449 (Trp64Arg/W64R) polymorphism being connected with low energy expenditure and the susceptibility for developing obesity (13-15).

Apart from the polygenic obesity, a number of over 60 genetic monogenic and pleiotropic genetic syndromes describe obesity as their main and only or one of their main clinical features. Several genes have been identified as the mutational causal factor for monogenic obesity syndromes (leptin, proopiomelanocortin, melanocortin 4 receptor, prolactin, etc.) (16, 17), while more than 30 pleiotropic multisystemic syndromes have been reported of including obesity (Prader Willi syndrome, Alstrom syndrome, Cohen syndrome, Fragile X syndrome, etc.) (18, 19).

The Romanian population has showed during the past years an alarming increase in the incidence of obesity in all races, sexes, social, cultural, religious or geographic environments. The high rates of this disorder in children notable should inquire immediate action from the scientific and medical worlds in order to finally fully understand and try to cutback the development of this dangerous disease.

2. Purpose of the study

The current study wishes to emphasize the frequency of the FTO rs9939609 and ADRB3 rs4994 genetic variants in our Romanian (Caucasian) cohort. The research also intends to detect the correlation between these gene polymorphisms and the obesity susceptibility. These estimations would represent a first step in providing a genetic risk map for this disorder in our Romanian population.

3. Materials. Methods
3.1. Cohort selection

Our study included a total of 64 subjects seperated into: 1. Adults, 33 individuals (23 obese, 10 normal/controls); 2. Children, 23 subjects (13 obese, 10 normal/controls); 3. Prader-Willi syndrome patients (8). The whole research consisted in a number of different association studies between the obesity pathogenesis and predisposition and each of the FTO rs9939609 and ADRB3 rs4994 (Trp64Arg) gene variants: adults study, children study, PWS patients study, family study, whole cohort study.

The present paper adresses the frequencies study of both the FTO rs9939609 and ADRB3 rs4994 polymorphisms in our groups.

3.2. Biological material

FTO rs9939609 and ADRB3 rs4994 (Trp64Arg) DNA genotyping were performed on DNA extracted from saliva and blood. All selected subjects have given their written informed consent for the procedures and any further use of their biological material and data. the study has been conducted under the supervision and with the approval from the Bioethics Committee of the National Commission of Romania for UNESCO.
3.3. DNA genotyping method
The method used for both polymorphisms genotyping was the High Resolution Melting Quenching Probe’s temperature (HRM-QP) analysis performed on an Arkray I-Densy 5320 system. IsoHelix Buccal Swabs and Isolation Kits were used for collecting and isolating saliva for DNA extraction.

3.4. Statistical analysis and association studies
Data and results obtained through genotyping were analysed with the use of the statistics SPSS software (version 13.0) and the Microsoft Excel Analyse-it Tool Pack 1.71. For the present study the Descriptive (Frequencies, Ratios) and ANOVA analysis were approached.

4. Results
All allele frequency results for the FTO rs9939609 and ADRB3 rs4994 genotyping are listed in table 1 (figures 1, 2).

5. Discussions
5.1. FTO rs9939609 genotyping (figure 1).

![Figure 1. FTO rs9939609 mutant A allele worldwide and Romanian cohort frequencies map (after 12)](image)

5.1.1. FTO rs9939609 genotypes and mutant A allele frequencies in all subjects
The FTO rs9939609 polymorphism is known to be a common gene variant in the Asian (84%, with an overall global high in Southern Han Chinese – 86%) and Latin American (72%) populations, while being less widely spread in African individuals (46%). In Caucasians, 58% of the Europeans carry the mutant A allele, with highest incidence in the Iberian population (64%) (10, 12).

In all the subjects from our study the frequency of the A allele was 71.9%, 7.9% higher than the overall worldwide reported frequency of the allele (64%) and 13.9% higher than the European Caucasian one (58%) (12), 46 out of the total of 64 individuals carrying at
least one copy of this genetic variant. The incidence of this mutant allele in the obese subjects (adults and children) was as high as 88.9% (PWS patients not included), with almost half of the obese individuals (47.2%) carrying the homozygous mutant (AA) genotype, while in all the controls A allele was identified in just 40% (10% AA).

Although the number of individuals in the present research is not big enough to make general assumptions, the high rate of the A allele in our study group may be an indicator that the rs9939609 SNP of the FTO gene is a common genetic variant in the Romanian (Caucasian) population, with an elevated correlation with obesity and the predisposition for developing this disease.

Table 1. FTO rs9939609 A allele and ADRB3 rs4994 C allele frequencies

| SNP         | GENOTYPE     | ADULTS   | CHILDREN | TOTAL (AD+CH, no PWS) | PWS | TOTAL  
|-------------|--------------|----------|----------|-----------------------|-----|--------
|             |              | OBESE    | NORM     | TOTAL                 |     |        
|             |              | Hm.     | wt       | Ht                   |     |        
|             |              | No.     | TT       | TA                   |     |        
|             |              | %       |          |                       |     |        
| FTO rs9939609 | Hm. wt TT   | 1       | 5        | 6                    | 3   | 4      
|             |              | 4.3     | 50       | 18.2                 | 23.1| 33.1 
|             |              | 9       | 3        | 12                   | 6   | 9      
|             |              | 43.5    | 30       | 36.4                 | 46.2| 39.1 
|             |              | 13      | 2        | 15                   | 4   | 4      
|             |              | 56.5    | 20       | 45.5                 | 30.8| 17.4 
|             |              | 23      | 10       | 33                   | 13  | 23     
|             |              | 69.7    | 30.3     | 51.56                | 56.5| 35.94 
|             |              | 87.9    | 12.1     | 61.5                 | 61.5| 88.9 
|             |              | 95.7    | 50       | 81.8                 | 76.9| 56.5 
|             |              | 95.7    | 50       | 81.8                 | 76.9| 56.5 
|             |              | 95.7    | 50       | 81.8                 | 76.9| 56.5 
|             |              | 23      | 10       | 33                   | 13  | 23     
|             |              | 69.7    | 30.3     | 51.56                | 56.5| 35.94 
|             |              | 87.9    | 12.1     | 61.5                 | 61.5| 88.9 
|             |              | 95.7    | 50       | 81.8                 | 76.9| 56.5 
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|             |              | 95.7    | 50       | 81.8                 | 76.9| 56.5 
|             |              | 23      | 10       | 33                   | 13  | 23     
|             |              | 69.7    | 30.3     | 51.56                | 56.5| 35.94 
|             |              | 87.9    | 12.1     | 61.5                 | 61.5| 88.9 
|             |              | 95.7    | 50       | 81.8                 | 76.9| 56.5 
|             |              | 95.7    | 50       | 81.8                 | 76.9| 56.5 
|             |              | 95.7    | 50       | 81.8                 | 76.9| 56.5 
|             |              | 23      | 10       | 33                   | 13  | 23     
|             |              | 69.7    | 30.3     | 51.56                | 56.5| 35.94 
|             |              | 87.9    | 12.1     | 61.5                 | 61.5| 88.9 
|             |              | 95.7    | 50       | 81.8                 | 76.9| 56.5 
|             |              | 95.7    | 50       | 81.8                 | 76.9| 56.5 
|             |              | 95.7    | 50       | 81.8                 | 76.9| 56.5 
|             |              | 23      | 10       | 33                   | 13  | 23     
|             |              | 69.7    | 30.3     | 51.56                | 56.5| 35.94 
|             |              | 87.9    | 12.1     | 61.5                 | 61.5| 88.9 
|             |              | 95.7    | 50       | 81.8                 | 76.9| 56.5 
|             |              | 95.7    | 50       | 81.8                 | 76.9| 56.5 
|             |              | 95.7    | 50       | 81.8                 | 76.9| 56.5 
|             |              | 23      | 10       | 33                   | 13  | 23     
|             |              | 69.7    | 30.3     | 51.56                | 56.5| 35.94 
|             |              | 87.9    | 12.1     | 61.5                 | 61.5| 88.9 
|             |              | 95.7    | 50       | 81.8                 | 76.9| 56.5 
|             |              | 95.7    | 50       | 81.8                 | 76.9| 56.5 
|             |              | 95.7    | 50       | 81.8                 | 76.9| 56.5 
|             |              | 23      | 10       | 33                   | 13  | 23     
|             |              | 69.7    | 30.3     | 51.56                | 56.5| 35.94 
|             |              | 87.9    | 12.1     | 61.5                 | 61.5| 88.9 
|             |              | 95.7    | 50       | 81.8                 | 76.9| 56.5 
|             |              | 95.7    | 50       | 81.8                 | 76.9| 56.5 
|             |              | 95.7    | 50       | 81.8                 | 76.9| 56.5 

5.1.2. FTO rs9939609 genotypes and mutant A allele frequencies in adults groups
The adults group revealed the highest FTO rs9939609 gene variant frequencies. The overall adults frequency of the A allele was 81.8% (27 out of 33 adults), with a booming 95.7% (22/23) in obese adults and 50% (5/10) in controls. The rate of the homozygous mutant (AA) and heterozygous (TA) genotypes was considerably higher in obese than in subjects (TA – 43.5% vs. 30%; AA – 56.5% vs. 30%), while only 4.3% (1/23) of these individuals were wearing the TT FTO genotype. These proportions and the important 45.7% statistical difference between the adults groups (p=0.024, ANOVA test) may be a proof that the FTO rs9939609 gene variant is a strong indicator for obesity and the predisposition for obesity in our Romanian Caucasian cohort.

Furthermore, these numbers are much higher than the worldwide and European frequencies and tend to be similar to those in which this mutant FTO allele is a high risk predictor for obesity (Asian and Latin American), possibly indicating themselves the higher predisposition of our group for developing this disorder.

5.1.3. FTO rs9939609 genotypes and mutant A allele frequencies in children groups

13 of the 23 children in our study were shown carrying the A allele (56.5%), frequency similar with the European Caucasian one (68%) (ensembl.org [12]), although revealing an unexpected difference to the high frequencies of this gene variant in the adults group (81.8%). This 13.8% difference correlated to the hugely 95.7% A allele rate in the obese adults may point out the fact that the rs9939609 FTO SNP has been identified more in association with obesity in adults than in children in our Romanian Caucasian cohort, while both being statistically linked with this disorder however.

Nevertheless, the obese group showed an elevated percentage (76.9%, 10/13) of the A allele, while the control (normal) children group reported the most surprisingly low rate of the A allele, 30% (3/10) and a 0% incidence of the AA homozygous mutant genotype, this genotype being represented in our cohort by the obese children only. As in the adults groups, the fact that there was such a considerable statistical (p=0.001, ANOVA test) difference (49.9%, close to the one found in the adults group) regarding the mutant FTO allele frequencies between the 2 children groups (obese/normal) may indicate that the FTO rs9939609 polymorphism has the same strong association with obesity in children as in adults, being much more common in obese children than in normal weight ones.

5.1.4. FTO rs9939609 genotypes and mutant A allele frequencies in PWS patients group

The Prader Willi patients revealed a slightly higher frequency of the A allele compared to the general study cohort (75% vs 71.9%). Although the low number of PWS individuals included in our research, 8, does not allow us to extend the frequencies to an at least isolated population status, we found it specifically interesting to observe the increased rate of the homozygous AA genotype, 50% (4 out of 8 patients), higher than the one found in obese subjects from both adults and children groups (47.2%), yet lower than the obese adults one (56.5%).

Being given the etiology of PWS however, we cannot link the obesity from this complex genetic disorder to the presence of the mutant FTO rs9939609 A allele, as it is the direct cause of a specific different kind of genetic mistake (lack of the satiety hypothalamic center due to a 15q11-13 microdeletion). It may be nevertheless intriguing to understand if obesity itself draws upon genetic mutations known to be associated to itself, this possibly being one of the multiple mechanisms in the case of the PWS patients in which the lack of this specific satiety center in the hypothalamic nuclei produces its effects upon body weight and fat mass.

5.2. ADRB3 rs4994 (Trp64Arg) frequencies (figure 2)
5.2.1. **ADRB3 rs4994 genotypes and C allele frequencies in all subjects**

The ADRB3 rs4994 polymorphism is known to be a rare gene variant worldwide in all populations (10%), with a possible interference in obesity pathogenesis and association with the energy pathway alteration in this disorder. The Asians are known to be more predisposed of carrying the mutant C allele (15%), with an overall global high in the Japanese population (21%), while being extremely rarely met in Africans (6%). In Caucasians, 8% of the Europeans carry the mutant C allele, with highest rates in the Italian Toscani population (18%) (13, 15).

![Figure 2](image)

In all the subjects from our study the frequency of the C allele was 18.8%, 8.8% higher than the overall worldwide reported frequency of the allele (10%) and 10.8% higher (more than double) than the European Caucasian one (8%) (15), 12 out of the total of 64 individuals carrying at least one copy of this genetic variant. Although still a rare ADRB3 variant, these numbers are much higher than the worldwide and European frequencies and tend to be similar to those in which this mutant FTO allele is a high risk predictor for obesity (Japanese Asian) (15), possibly indicating themselves the higher predisposition of our group for developing this disorder.

The incidence of this mutant C allele in the obese subjects (adults and children) was 25% (PWS patients not included), while the controls revealed no C allele (0%, 0/20). It is important to state that there have been no CC homozygous mutant genotype in any of our 64 subjects, invoking the rarity of this genetic variant. The fact that the only C allele carriers were found only in the obese groups (adults and children) may point out that the ADRB3 Trp64Arg polymorphism may be correlated with obesity and the predisposition for developing this disease in our study group and possibly in the Romanian population, while yet remaining a rare SNP in our cohort.

5.2.2. **ADRB3 rs4994 genotypes and C allele frequencies in adults groups**
The overall adults frequency of the C allele was 12.1% (4 out of 33 adults), with a higher rate in obese (17.4%, 4/23, all heterozygous, TC) than in controls (0%, 0/10). The important, although not statistical (p=0.17, ANOVA test), 12.1% difference between the adults groups may be a proof that the ADRB3 rs4994 gene variant is one of the markers for obesity predisposition in our Romanian Caucasian cohort.

5.2.3. ADRB3 rs4994 genotypes and C allele frequencies in children groups

5 of the 23 children in our study were shown carrying the C allele (21.7%), 0.7% higher than the overall high Japanese rate and close to triple than in the European Caucasian one (8%) (15), revealing at the same time an intriguing 9.8% (almost double) difference to the adults groups frequency (12.1%).

This contrast correlated with the extremely elevated 38.5% C allele rate in the obese children and the difference between the obese and adults children groups (38.5%) may point out the fact that the rs9939609 FTO SNP has a much stronger association with obesity in children than in adults in our Romanian Caucasian cohort.

5.2.4. ADRB3 rs4994 genotypes and C allele frequencies in the PWS group

The Prader Willi patients revealed an unexpectedly higher, more than double frequency of the C allele when compared to the general study cohort (37.5% vs 18.8%), 3 of the 8 subjects carrying the ADRB3 TC heterozygous genotype.

As stated before in previous paragraphs, PWS has a distinctive genetic cause which leaves little space for predisposition in the case of obesity, as this specific disorder is generated directly from the lack of the satiety brain center. Nonetheless, being given the high incidence of the mutant C allele in our 8 PWS patients, we may question whether the lack of this specific hypothalamic center generates obesity through different other genetic markers known to be involved in the hunger-satiety pathway. The study must however extend to a much greater number of subjects in order for such assumptions to be made.

5.3. Obesity genetic predisposition and eating behaviour and lifestyle

The FTO gene action on the fat mass (adipose tissue) accumulation is expressed by altering eating behaviour, control over eating and response to highly environmental hunger and hunger-like stimuli. In this respect, lack of control over eating (which seems to be directly influenced by the FTO gene variants and especially by the rs9939609 polymorphism), and also geographical, social, economical, psychological, political, religious, behavioural individuals aspects are all environmental risk factors for developing obesity (20). In this regard, early susceptibility screening for this disorder may deliver important benefits to persons carrying the genetic predisposition (represented by multiple obesity risk gene variants), as changing their eating habits and decreasing the environmental interference (mostly through sustained / lifetime diet and physical exercise) proved to deny or even cancel the genetic inheritance (21-23).

At the same time, FTO expression has been illustrated of altering or interacting with other chromosome locations known to be involved in the brain/hypothalamic hunger – satiety pathway. Thus, studying the specific rs9939609 polymorphism of the FTO gene and the rate in which this common general population variant is found in our Romanian study should provide, through association studies, clues on the mechanism in which different responses to hunger and various lifestyles can influence this predisposition in the extent of developing into the actual disorder.

Association study results showed complete concordance with reported literature regarding the role of the FTO gene in the obesity etiopathogenesis, proving that FTO rs9939609 genotyping is an effective prophylactic method of early detecting the susceptibility
for this disease and setting up a healthy lifestyle for counteracting the genetic influence to gain weight (3, 24-28).

Moreover, the high mutant A allele frequency and the increased rate of the AA homozygous mutant genotype in correlation with obesity not only in adults, but in children as well, should pull a high alarm signal towards studying this genetic variant.

Obesity is known to be the perfect risk terrain for the development of further severe complex disorders, such as: glucose metabolism alterations and diabetes mellitus, hypertension, heart failure, embolism, stroke, atherosclerosis, kidney failure, hepatic steatosis, dislipidemias and other lipid metabolism disfunctions, metabolic syndrome, basal metabolic rate and energy metabolism alterations, etc. These are direct consequences and often comorbidities of obesity. Once having its debut during childhood, long term weight gain, sustained obesity and its persistence into adulthood will be a far greater predisposal factor for all the above-mentioned diseases (29).

In our first ever approach of the ADRB3 rs4994 genotyping on the Romanian population, there has been shown that the mutant variants are very rare, so far for the our less than 100 individuals group. It has been elected together with FTO genotypes as being representative of the energy expenditure processes, and thus the final effect of the energy accumulation, a process controlled by FTO gene variants. The ADRB3 gene has shown to be a rare genetic variant in our Romanian population. This gene is expressed especially in the adipose tissue and is known of being associated with the regulation of lipolysis and thermogenesis, its rs4994 being highly associated with obesity predisposition in the Asian, especially Japanese population (30, 31).

There are however 2 other β-adrenergic receptors (ADRB1 and ADRB2), also linked with obesity risk, which may prove to be better genetic variants for future associative research in the Romanian population (several studies indicate correlations between different ADRB2 SNPs and obesity in European Caucasian populations). Further approach of more genetic variants of adrenergic receptors on a more numerous individuals may have a substantial potential to correctly correlate their role in obesogenic genetic field in our population.

The adipose tissue expression of the ADRB3 gene and its possible interference or positive co-regulation with the FTO gene’s fat mass activity persuaded us upon the Asian stated genetic variant of ADRB3. Nonetheless, the fact that the mutant C allele of the rs4994 ADRB3 SNP has been scarcely identified in our cohort does not imply that this polymorphism shows no correlations with obesity. On the contrary, while not statistically significant due to the low number of C allele carriers among our study groups, the association with the obesity risk is to be surveyed as all the rs4994 heterozygotes (TC; no CC genotypes identified in our cohort) belonged to the obese groups and none of the controls were identified of wearing this allele.

Yet, recent research comes in our approval and shows similar results but with statistical associative significance in this case in a Hungarian cohort. (32).

The wider research, out of which the current study was extracted, has been the first ever evaluation of the genetic predisposition for the common obesity, both gene variants (FTO rs9939609 and ADRB3 rs4994) never having been genotyped before in association with this disorder in our country. While the ADRB3 gene was never described before in Romania, only one research approached the FTO gene before, yet not in correlation with obesity (33).

6. Conclusions

The rs9939609 FTO polymorphism is a common genetic variant among the studied Romanian Caucasian cohort. The mutant FTO A allele has been described in high frequencies
in the obese individuals from our study, being strongly correlating with obesity. Our research revealed high rates of the homozygous mutant (AA) genotype, especially in the obese groups. Although statistically significant in both groups, the A allele was more associated with obesity in adults than in children.

The ADRB3 rs4994 polymorphism is a rare genetic variant in our Romanian cohort. The C allele of the ADRB3 gene has shown correlations, although not statistical, with obesity susceptibility, all of the heterozygous (TC) individuals belonging to obese groups, while no homozygous mutant (CC) subjects were reported. Although rare, the ADRB3 Trp64Arg SNP’s frequency was higher in our Romanian groups than in the reported worldwide population. In contrast with the FTO rs9939609 A allele, the ADRB3 rs4994 C allele has pointed out a higher association with the predisposition for obesity in children than in adults.

The frequency of the FTO A allele in Prader Willi syndrome patients was close to the general population one, with a high incidence of the AA genotype, possibly indicating a role of this genetic variant in the pathogenesis of obesity in this syndrome. The frequency of the ADRB3 C allele in PWS subjects was much higher than in the other studied groups and than in the reported worldwide rates, opening a possible debate in the respect of this SNP’s implication in the development of obesity in PWS patients.

Knowing the frequencies in which a genetic variant with clinical implications is present in a specific population is of extreme importance in the full and correct understanding of the complex molecular mechanisms which lead to the development of the different disorders.

The rs9939609 FTO gene polymorphism has been proven in our cohort of being a strong, widely spread, indicator for obesity susceptibility. While seemingly rare, the rs4994 ADRB3 when present is a fair predictor of the predisposition for developing obesity.

Further studying of these genetic variants on broader cohorts would be of great importance in decrypting the molecular pathways involved in the etiopathogenesis of obesity.

This current frequency study and the positive associative results are of great importance for clinical practice and management of obesity, as the FTO rs9939609 gene polymorphism mainly and, at some extent, the ADRB3 rs4994 SNP as well, when present, are significant indicators for the predisposition to develop this disorder.

The present results from DNA genotyping and the statistical differences in mutant alleles frequencies between obese and normal individuals in our study groups have provided us a secure set-off point for association studies with the commonly reported clinical obesity parameters (weight, waist, body mass index, basal metabolic rate, body fat mass and excess) and with the biological markers for various obesity comorbidities (lypids, glucose, transaminases, thyroid hormones, blood pressure).

These correlations are yet to be published and tend to provide precious information on the future possibility of an early obesity risk detection and management.

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