THE INFLUENCE OF THE RS7566605 IN OVERWEIGHT IN DIFFERENT POPULATIONS - A SYSTEMATIC REVIEW

Caíque Almeida Costa*, Caroline Feitosa**, Geraldo Ferraro***

Corresponding author: Geraldo Ferraro - geraldo.ferraro@bahiana.edu.br
* Biomedicine undergraduate student in BAHIANA - School of Medicine and Public Health
** Phd Student in Public Health in the Federal University of Bahia, professor at BAHIANA - School of Medicine and Public Health
*** Professor at the BAHIANA - School of Medicine and Public Health

Abstract

Introduction: Obesity and overweight are major worldwide public health problems associated with several etiological factors. The rs7566605 polymorphism in the INSIG-2 gene is reported to be associated with the development of obesity. This polymorphism occurs when there is a change in the nitrogenous base guanine (G) for cytosine (C) resulting in two possible mutant genotypes: CC and CG. The wild genotype is represented by GG. Many authors reported the association between this polymorphism with anthropometrical changes, but there is no consensus regarding this issue. Objective: to evaluate the frequency of rs7566605 polymorphism and its association with obesity markers in populations from different geographical areas. Method: systematic review using PubMed and following the PRISMA Guidelines. Results: there was a great variability in terms of sample size, areas, bias and phenotypic characteristics. Although 38 biological traits were evaluated, the mutation was associated with only three of them (BMI, Waist-Hip Ratio, HbA1c). The highest CC frequency was found among obese Malays (21%), and the lowest among overweight Quilombo people (3%). The highest CG frequency was found in non-obese Malays (51%), while the lowest was reported among overweight Quilombo people (22%). Also, Quilombo people reported the highest frequency of the GG phenotype (75%), while the lowest frequency was found in non-obese Malays (32%). Conclusion: The polymorphism was associated with only three obesity markers. There were specific patterns of genotypic frequency among populations belonging to similar geographical areas and/or ancestry. More research into the genetic factors related to obesity markers is needed.

Keywords: INSIG-2; rs7566605; Obesity.
INTRODUCTION

According to the World Health Organization (WHO) obesity and overweight are defined as an abnormal or excessive fat accumulation\(^1\) which are associated with the development of several diseases such as diabetes, hypertension, congestive heart failure, cardiovascular and coronary heart disease.\(^{2-5}\) In 2014, more than 1.9 billion of adults over the age of 18 were classified as overweighted, and more than 600 million of those were obese.\(^6\) Its prevalence has been increasing over the years,\(^{1,6,7}\) and it is defined as a multifactorial phenomenon related to genetic and environmental factors.\(^8,9\)

Many genes are reported to be related to the development of obesity in human populations.\(^10-14\) Among those, the rs7566605 polymorphism in the insulin-induced gene 2 (INSIG-2) is described as a potential etiological factor.\(^11\) This polymorphism occurs when there is a change in the nitrogenous base guanine (G) for cytosine (C), which is located 10 Kb upstream of INSIG-2, resulting in two possible genotypes: CC mutant homozygous and CG heterozygous. The wild genotype is represented by GG.\(^15\) At high sterol concentrations the insig-2 protein inhibits the production of triglycerides, phospholipid, cholesterol and unsaturated fatty acid.\(^16,17\) It is speculated that the rs7566605 can impact this process, but it is still unclear.\(^11\)

Despite the fact that several previous studies have reported an association between the rs7566605 polymorphism and anthropometric changes,\(^11,14,18-21\) others have shown no association at all.\(^18,23,24-32\) The controversial results of these works call for a systematic review for a better understanding of the role of this polymorphism in obesity. Furthermore, there is a scarcity of literature review on this subject. The aim of this study is to systematically review the literature on the distribution of rs7566605 polymorphism in different populations from several geographic areas and its relationship with obesity.

METHODS

This systematic review was prepared following the PRISMA Guidelines.\(^33\) A survey of full text papers in English on the electronic database Pubmed was carried out using the following algorithm Search “obesity AND (INSIG-2 OR rs7566605) Filters: Publication date from 2010/12/18 to 2014/12/18”. The keywords were INSIG-2, rs7566605, and obesity. The identification and inclusion of papers was performed by two reviewers, and there was no disagreement (figure 1).

![Figure 1 - PRISMA Flow Diagram](image-url)
**Eligibility criteria:** For this review, we included papers that presented the following characteristics: (1) Original articles, (2) with human participants of any age group, any gender and from different countries, (3) with assessment of the genotype frequencies and phenotype variables related to obesity.

**Data items:** Information was collected from all papers such as: (1) Characteristics of participants (age, ethnicity, genotype frequencies for rs7566605 polymorphism); (2) Characteristics of the study (study type, follow-up time for the cohort studies, number of participants); (3) Associated variables (figure 2).

**Figure 2 - Phenotypic characteristics related to obesity**

Phenotypic characteristics related to obesity are organized in circles with proportional sizes, according to the amount of citations. Circles filled with gray color represent the characteristic studied with no significative association in the studies. Circles colored inside, represent characteristics associated. Digits inside the circle are the reference number. P-values are reported along with the colored circles. BMI- Body mass index. TSH- Thyroid-stimulating hormone. SBP- Systolic blood pressure. DBP- Diastolic blood pressure. NEFA- Non-esterified fatty acids, HDL-C- High-density lipoprotein cholesterol. LDL-C- Low-density lipoprotein cholesterol. ALT- Alanine aminotransferase. AST- Aspartate aminotransferase. GOT- glutamic oxaloacetic transaminase. HbA1c- hemoglobin A1c. Adapled.

**Summary measures:** There was a lack of agreement between the measures of association reported among the different studies. The p-value was the main measure to assess the association between the studied mutation and the variables related to obesity, because it was reported in all the selected studies.

**Additional analyses:** For the papers which did not report the genotypes, the frequency was calculated using the crude data from the result section provided by the papers. These frequencies are presented in graph 1.
Graph 1 - Genotypic frequencies of the rs75666605 among different populations

Numbers inside columns represent the percentage of the genotypes. CC-Mutant Homozygous, CG- Wild Heterozygous, GG- Wild Homozygous; Numbers inside the parentheses (n) represent the reference number. Groups of study are inside square brackets [ ]. For some papers, the genotype percentage was calculated by the authors*¹ Genotypic frequency provided by the author via e-mail.*² Ethnicity provided by the author via e-mail.

RESULTS

After reviewing and applying the inclusion and exclusion criteria, 13 papers were screened and 9 papers were selected. From the 13 papers, 2 were excluded because the title did not contain the keywords and other 2 papers because they did not investigate the rs75666605 polymorphism, leaving 9 papers for complete analysis (figure 1).

The selected studies used different study designs, including case-control, cross-sectional and cohort studies. The studies included 16,617 obese and non-obese participants with a BMI (Body Mass Index) ranging from 19.9 ± 4.8 to 50.2 ± 8.8, from different geographical areas (graph 1), with ages from birth to 74 years old (table 1). The follow-up time of the cohorts ranged from 2 to 26 years (data not shown). The rs75666605 polymorphism frequency was assessed in the different papers (graph 1). Furthermore, 38 parameters related to obesity were investigated, such as: biochemical parameters related to diabetes and hypertension, hematological, biochemical, renal, and hepatic parameters, behavior disturbances, anthropometrical measures and hormones (figure 2). From those, only 3 (BMI, WHR - Waist-Hip Ratio and HbA1c - Glycated Haemoglobin) were associated with the presence of the polymorphism (figure 2).
Table 1 - Details of the studies reviewed: sample information and study design

<table>
<thead>
<tr>
<th>Source</th>
<th>Country</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Age Range (in Years)</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burgdörfer et al., 2013</td>
<td>Germany</td>
<td>Case Control</td>
<td>124</td>
<td>39.7</td>
<td>BMI·40</td>
</tr>
<tr>
<td>Malzahn et al., 2014</td>
<td>Germany and USA</td>
<td>3 Cohorts KORA S3/F3 KORA S4/F4 FHS-Off</td>
<td>6926</td>
<td>25-74</td>
<td>BMI·30</td>
</tr>
<tr>
<td>Angeli et al., 2011</td>
<td>Brazil</td>
<td>Cross-sectional</td>
<td>331</td>
<td>&lt;17 years</td>
<td>BMI·25</td>
</tr>
<tr>
<td>Gaifen et al., 2011</td>
<td>Georgia</td>
<td>2 Cohorts Georgia CV Twin study BP Stress study</td>
<td>1592</td>
<td>10-25.8 (Euroamerican) Twin study Men 21.2 ± 5.1 Women 21.3 ± 4.6 BP Stress Study Men 19.9 ± 4.8 Women 19.9 ± 5.4</td>
<td></td>
</tr>
<tr>
<td>Apalasamy et al., 2014</td>
<td>Malaysia</td>
<td>Case Control</td>
<td>672</td>
<td>Non obese 46.47 ± 7.06 Obese 47.97 ± 6.05</td>
<td>BMI·30</td>
</tr>
<tr>
<td>Barth et al., 2012</td>
<td>Germany</td>
<td>Case control</td>
<td>68</td>
<td>23-69</td>
<td>BMI·30</td>
</tr>
<tr>
<td>Baylin et al., 2013</td>
<td>American Samoa and Samoa</td>
<td>Cohort</td>
<td>717</td>
<td>22.55</td>
<td>Samoa Men 29.2 (5.0) Women 31.1 (5.1) American Samoa Men 33.9 (6.0) Women 35.9 (7.1)</td>
</tr>
<tr>
<td>Manish et al., 2013</td>
<td>USA</td>
<td>Cohort</td>
<td>1276</td>
<td>41.8 (Hispanics) 46.1 (American*)</td>
<td>American*: 50.2 ± 8.8 Hispanics 44.7 ± 6.4</td>
</tr>
</tbody>
</table>

Notes: USA - United States of America *Information provided by the autor by e-mail**Information from the supplementary informations from article.

Together, all the studies included a total of 16,617 patients from different areas, who were genotyped for the rs7566605 polymorphism (graph 1). The study of the allele frequencies shows a higher frequency of the GG genotype (higher than 50%) in African descendents (Quilombo people and African-American), while the lowest frequencies were identified among Malays (32-33%). On the other hand, for CC genotype, the lowest frequencies were found among African descendents and Hispanics (3-8%), while the highest were reported among Malays and American Samoaan women (15-21%). The “German, European-American and Norwegian” groups showed similar frequencies (approx. 11.5%) for the CC genotype. The highest frequency of the GC genotype was reported among
Malays/Samoas (46-51%) and the lowest among African descendants (22-39.5%).

DISCUSSION

This systematic review attempted to understand the association between the rs7566605 polymorphism with phenotype parameters and its frequencies among populations from several geographical areas. Nine papers were found, reporting and comparing the frequencies of genotypes from different populations. Three papers showed an association with some phenotypic parameter, especially BMI, WHR, and Hba1c.(20-22)

Although several phenotype traits were investigated, BMI was the single parameter assessed in all studies. However, only one study(22) reported an association between the rs7566605 polymorphism with an increase in BMI. This could be explained by the method used by these authors, who investigated this polymorphism in a gene interaction process with the polymorphism rs2229616 from the MC4R gene, unlike other authors who analyzed the polymorphism rs7566605 individually.

Controversial findings were found for the WHR. One study(21) identified a positive association between the C allele with WHR in Norwegian adolescent males (13 to 19 years old) and adults (24 to 30 years old). On the other hand, another study(20) demonstrated that the presence of the CC genotype from the rs7566605 polymorphism was associated with a lower WHR in Germans aged on average 39.7 years. Furthermore, no association was found among Quilombo people older than 17, as well as among European-American and African-Americans aged between 15 and 26 years. These controversial findings may arise from the ethnic differences between the studied populations. Another study(21) suggests that WHR measure changes according to the population studied without, however, reflecting a direct association with the amount of body fat.

The HbA1c rates were assessed only by one study, who found an association between the CC genotype with lower levels of Hba1c. The lack of further investigation involving this character and the polymorphism makes comparison with other papers very difficult. The pattern of genotype frequency of the rs7566605 polymorphism presented in all studies is corroborated by the literature. Similar frequencies among population groups from nearby geographical areas or with possible similar ancestry were also reported by the International Project HapMap(38) which aimed to catalog the genotype profile in different populations worldwide. These findings were also corroborated by other study(40) reporting specific genetic variations among populations with a common ancestry and among those who live in nearby geographical areas.

Another highlighting result was the difference between the genotype frequency for men and women reported among Samoan and American-Samoan populations. This difference was not expected because the INSIG-2 gene is located on an autosomal chromosome, with no expected difference for gene segregation regardless of the gender. Furthermore, it is worth emphasizing that this reported difference can arise by chance, and it is not necessarily statistically significant, mainly because of the small sample size in the mentioned study. This limitation was recognized by the author herself.(35)

The genotype frequency for the African descendants compiled in this paper are similar to the genotypic frequency analyzed in Africans in the Hapmap Project. It is possible that the differences among the genotype frequencies on different populations may be explained by evolutionary aspects related to natural selection, as shown in a recent literature review, which demonstrated several genes possibly related to the process of natural selection.

STRENGTHS AND LIMITATIONS OF THE REVIEW

There are some limitations regarding the results reported in this study which should be taken into account. This is not a population study, consequently, this work is not affordable to determine the real genotype frequency of populations from different geographical areas. In addition, this review was limited to papers in English indexed in Pubmed.
Furthermore, there is a lack of studies including representative populations from other areas, such as South America, Africa, Asia and Oceania. The reviewed papers contained important limitations, such as small sample size, selection bias, lack of control for important confounders such as age, participants’ diet, use of medicines, genetic ancestry, as well as possible measurement error in the anthropometric variables. The papers also showed great variability in the age groups and reported variables, making comparison difficult.

Despite these limitations, this paper is the first attempt to compare the results from different studies, combining the genotype frequency from different populations. An understanding of the mutation distribution of genes potentially related to the obesity pandemic may improve the scientific knowledge about this phenomenon. It could also lead to new strategies for the investigation of genetic factors in the etiology of obesity, a multifactorial disease. Available preventive strategies have been unable to reduce its increase.

CONCLUSION

Despite the conflicting results among the investigated studies, this review shows an association among the rs7566605 polymorphism with three main traits: BMI, WHR, HbA1c. The assessment of genotype frequencies showed specific patterns among populations belonging to similar geographical areas and/or ancestry. To our knowledge, this is the first review of the genotype frequency of the rs7566605 polymorphism in different populations and its association with obesity markers. The results of this work demonstrate the need for more research on the genotype frequency distribution, as well as possible associations with phenotype markers related to obesity.

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