

MSc in Bioinformatics

Master Thesis

**Detection of obesity susceptibility GENOMIC variants in Spanish population using sequencing data**

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# Acknowledgments

# Approval and signature

# Abstract

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# Introduction

## Obesity

Obesity is a medical condition that is defined as excessive accumulation of fat that is sufficient to adversely affect health1,2. According World Health Organization (WHO), people with a body mass index (BMI; weight in kg/height in m2) higher than 30 kg/m2 are considered obese and higher than 25 kg/m2 are considered overweight. The 30% of Americans and 10%–20% of Europeans are classified as obese, with the prevalence rising in many developing countries1. Being overweight or obese can have a serious impact on health. Carrying extra fat leads to serious health consequences such as cardiovascular disease (mainly heart disease and stroke), type 2 diabetes, musculoskeletal disorders like osteoarthritis, and some cancers (endometrial, breast and colon). These conditions cause premature death and substantial disability3.

### Obesity in Spanish population

The 26.6% of adult population in Spain are considered as obese and 62% are overweight. Furthermore, in Spanish childhood population, the prevalence of obesity has been increasing in recent years to such a stent that, the prevalence has increase until 18.3% among children (0-9 years of age) and 30% among adolescents (10-19 years of age). This data has made Spain be considered by WHO as one of the countries with the highest prevalence of obesity and overweight4.

## Causes of obesity

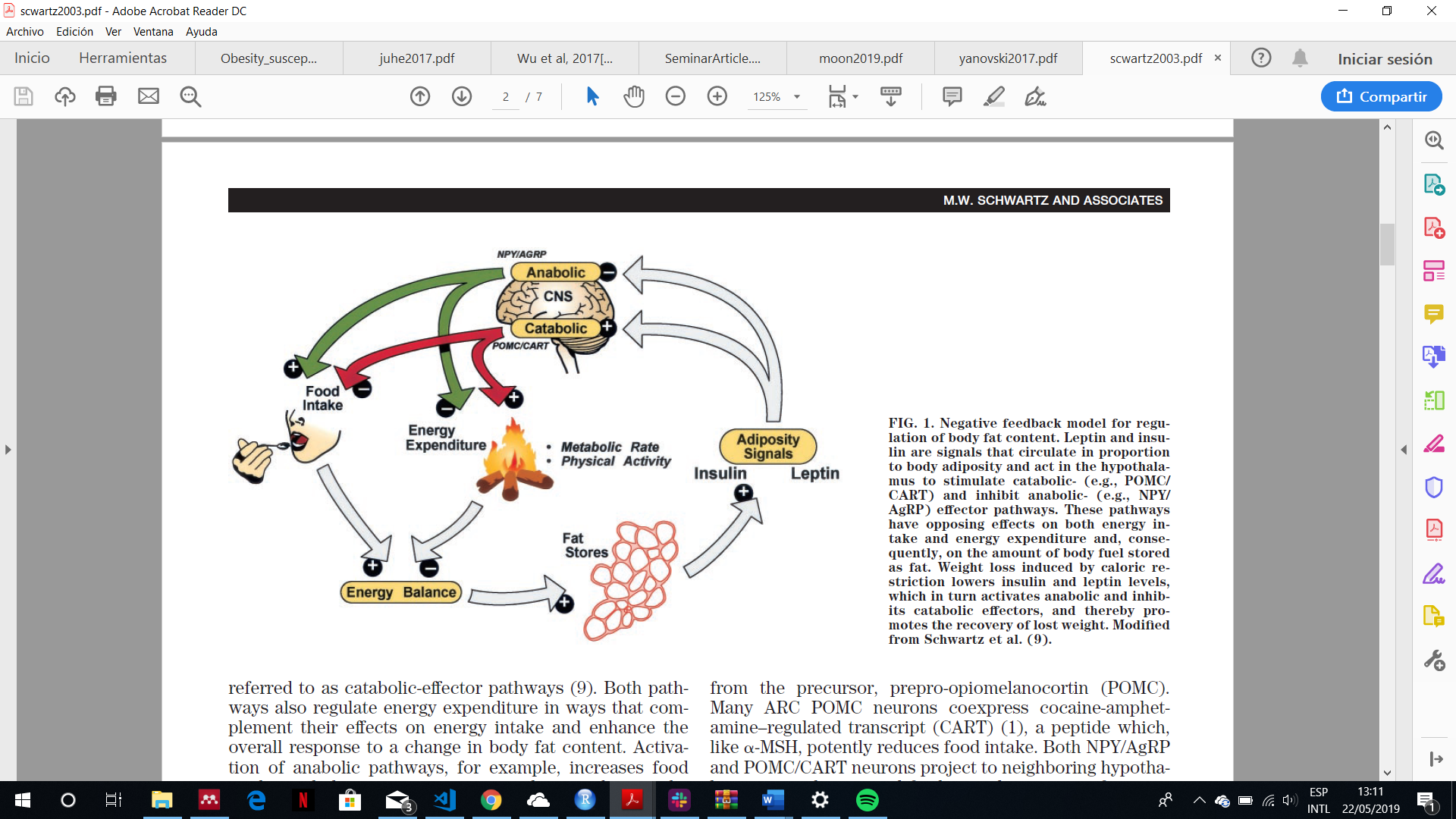
### Body weight control

The humans are able to regulate their body weight over long periods of time despite day-to-day variation in the number of calories consumed and in levels of energy expenditure1. The maintenance of constant body weight and body composition requires two conditions be met. [1] An even energy balance must be attained, i.e. energy expenditure must on average be equal to energy intake. [2] There must be an even balance for each individual substrate, i.e. protein, carbohydrate and fat oxidation must be equal to protein, carbohydrate and fat intakes respectively If this state were not present, body composition would inevitably change, even during isoenergetic feeding. If energy intake continuously exceeds energy expenditure, the excess energy ingested has to be deposited in order to increase the nutrients stores.

There is clearly a ‘hierarchy’ in substrate oxidation during overfeeding. Any increase in protein intake will rapidly lead to stimulation of protein oxidation, restoring a steady protein balance. The same is true for carbohydrates, the oxidation of which increases over 1–3 d to match any increase in carbohydrate intake. The result of this hierarchy is that excess energy intake leads essentially to fat storage, mainly in subcutaneous and visceral adipose tissue. In contrast, a period of hypoenergetic feeding will lead to a negative fat balance and a loss of adipose tissue1,5.

### Molecular pathway of energy homeostasis

Pathways that stimulate food intake and promote weight gain are referred to here as anabolic-effector pathways, whereas those that promote anorexia and depletion of body fat are referred to as catabolic-effector pathways. Both pathways also regulate energy expenditure in ways that complement their effects on energy intake and enhance the overall response to a change in body fat content. Activation of anabolic pathways, for example, increases food intake and decreases energy expenditure, whereas the reverse is true for catabolic pathways. Anabolic and catabolic pathways are generally regulated in a reciprocal manner, such that increases in the activity of one are often accompanied by decreases in the other. The anabolic and catabolic pathways sense changes in energy balance due to the hormones leptin and insulin that circulate on blood proportionate to body fat mass and enter into the brain, where they bind to an and activate their respective receptors on the plasma membrane of targets neurons. Low concentrations of leptin and insulin increase energy intake and reduce energy expenditure. Hence, the reciprocal nature of the neuronal response to an energy deficit (activation of anabolic pathways and inhibition of catabolic pathways) may be accounted for, at least in part, by reduced levels of these two hormones (Figure 1).



**Figure 1: energy balance pathway.** This model controls the body fat mass storage. When the food intake increase, the excess of energy is stored at adipocytes. Once the adipocytes have stored energy in form of fat, they produce leptin that activate central nervous system pathways that stimulate the decrease of energy intake (satiety signals) and the increase in energy expenditure.

### Disorder of energy homeostasis

Disorders of energy homeostasis are fundamentally due to factors that disrupt the balance between energy intake and expenditure over time, the utilization of substrates (fat, protein, carbohydrate), and/or nutrient partitioning (storage of excess calories). The environmental influences of weight gain such as the adoption of sedentary lifestyles due to reduced physical activity at work and in leisure time coupled with an abundance of easily available, energy-rich, highly palatable foods represents a nutrition transition that, according with the WHO, is now one of the greatest factors to ill health worldwide1.

Other factor that disrupt the energy homeostasis is the genetic. In any environment, either energy rich or energy lacking, there are considerable distribution of different body weight among people. This evidence says that not only environmental factors cause obesity but also genetics factors1,2,6–8.

## Importance of genetics in obesity

The genetic contribution to body weight has been established through family studies, investigations of parent-offspring relationships, and the study of twins and adopted children9,10. These studies estimate a heritability (Fraction of the total phenotypic variance of a quantitative trait attributable to genes in a specified environment) of 40-70%. This genetics predisposition has been widely recognized in the human evolutionary history. Obesity stem from natural selection on our ancient ancestors favouring “thrifty genes”, defined as conferring a phenotype of being extremely efficient keeping all extra energy during periods of food abundance in order to deal with large famine periods. In modern society, however, with plentiful and continuous food, this thrifty phenotype process deleterious because it promotes efficient storage of fat for a famine period that never comes1,11.

## Obesity susceptibility variants

# Objectives

**Hemos intententado maximizar el poder para encontrar variantes al elegir unos individuos con extrema obesidad.**

# Material and Methods

## Data description

## SNV detection

### Variant Calling

### Significant variants detection

## CNV Analysis

# Results

# Discussion

# Conclusion

# Bibliography

# Appendix