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Review:

Genetics of Obesity

"Obesity Causes"

Hanan Ramadan Hamad Mohamed*

Zoology Department, Faculty of Science, Cairo University, Giza Egypt; *: Correspondence to: hananeey@sci.cu.edu.eg

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Abstract

Obesity is a complex and heterogeneous disorders characterized by excessive body mass and fat and determined by genes, environmental factors and also the interaction between genes and environment. With an increased incidence in children and a prevalence of up to 25% in some countries, obesity is becoming a clinical and public problem of increasing importance in modern society. Thus, in this review the causes of obesity in particular the genetic causes will be discussed.

Keywords: Obesity; Causes; Genetics causes; Inheritance.

1. Obesity

Obesity is a complex, heterogeneous group of disorders that is determined by genes, environmental factors and interaction between genes and environment, and characterized by excess body mass and fat **(Nirmala *et al*., 2008; González-Muniesa e al., 2017).** It is becoming an increasingly important clinical and public health problem in modern societies, with a prevalence of up to 25% in certain countries and an increasing incidence in children.

Obesity like any disease comes about as a malfunction of one or more of your bodies systems, and results from a net imbalance between calorie intake and energy expenditure. Many Americans are at increased health risk because they are obese. The U.S. Surgeon General, in a 1988 report on nutrition and health, estimated that **one-fourth of adult Americans** are overweight **(Mhtml:file://F:\OBESITY\Genetic%20Obesity.mht)**. It is characterized by an excessively high amount of body fat or adipose tissue that varies from individual to individual.

Obesity is increasing worldwide at an alarming rate in both developed and

developing countries. This is matter of concern because obesity increases risks for many serious and morbid diseases including heart disease, diabetes, high blood pressure, stroke, and some forms of cancer. Obese men are more likely than non-obese men to die from cancer of the colon, rectum, and prostate. Obese women are more likely than non-obese women to die from cancer of the gallbladder, breast, uterus, cervix, and ovaries **(Nirmala *et al*., 2008)**.

Its risk is about two to three times higher for an individual with a family history of obesity and it increases with the severity of obesity. Obesity is a major chronic disorder affecting 20-40% adults in India. Other diseases and health problems linked to obesity include: **gallbladder disease and gallstones**, **osteoarthritis** (a disease in which the joints deteriorate, possibly as a result of excess weight on the joints) and **gout** (another disease affecting the joints Pulmonary (breathing) problems, including sleep apnea, in which a person can stop breathing for a short time during sleep) **(Mhtml:file://F:\OBESITY\Genetics%20 obesity 1.mht)**.

Doctors generally agree that the more obese a person is the more likely to have health problems, and obesity is not just a cosmetic problem. It's a health hazard. Someone who is 40 percent overweight is twice as likely to die prematurely as an average-weight person. (This effect is seen after 10 to 30 years of being obese).

This means that, obesity is more than simply being overweight. Statistics show that the condition leads to many other health risks and its complications range from mild to severe. Some are even life threatening. Type 2 Diabetes, for instance, is a major threat to the obese, along with heart ailments and strokes, which can be fatal **(Mhtml:file://F:\OBESITY\Genetics%20 obesity 1.mht)**.

2. Obesity measurement

Everyone needs a certain amount of body fat for stored energy, heat insulation, shock absorption, and other functions. As a rule, women have more fat than men. Doctors generally agree that men with more than 25 percent body fat and women with more than 30 percent body fat are obese. Precisely measuring a person's body fat, however, is not easy. The most accurate method is to **weigh a person underwater** - a procedure limited to laboratories with sophisticated equipment.

There are two simpler methods for estimating body fat, but they can yield inaccurate results if done by an inexperienced person or if done on someone with severe obesity. **One** is to measure skinfold thickness in several parts of the body. **The second** involves sending a harmless amount of electric current through a person's body (bioelectric impedance analysis). Both methods are commonly used in health clubs

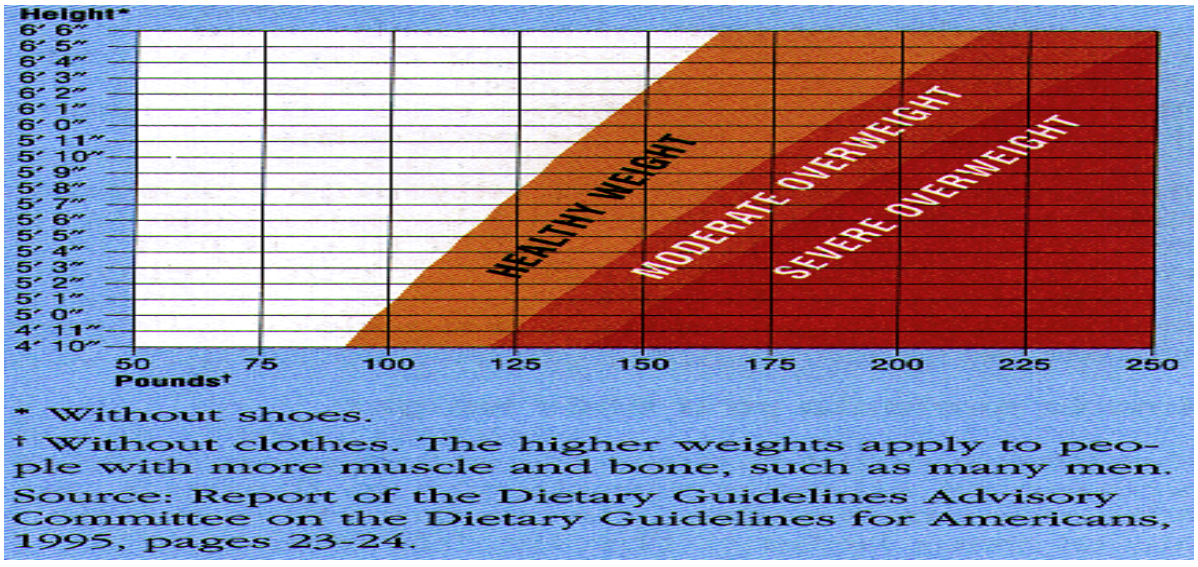
and in commercial weight-loss programs, but results should be viewed skeptically **(O'Rahilly and Farooqi, 2006; Etchison et al., 2011).**

Because measuring a person's body fat is tricky, doctors often rely on other means to diagnose obesity. Two widely used measurements are **weight-for-height tables** and **body mass index**. While both measurements have their limitations, they are reliable indicators that someone may have a weight problem. They are easy to calculate and require no special equipment.

2.1 Weight-for-Height Tables:

Most people are familiar with weight-for-height tables. Doctors have used these tables for decades to determine whether a person is overweight. The tables usually have a range of acceptable weights for a person of a given height.

One problem with using weight-for-height tables is that doctors disagree over which is the best table to use. Many versions are available, all with different weight ranges. Some tables take a person's frame size, age, and sex into account; others do not. A limitation of all weight-for-height tables is that they do not distinguish excess fat from muscle. A very muscular person may appear obese, according to the tables, when he or she is not. Still, weight-for-height tables can be used as general guidelines **(Mhtml:file://F:\OBESITY\Genetic%20Obesity.mht)**. The table printed here is from the 1990 edition of Dietary Guidelines for Americans, a pamphlet printed jointly by the U.S. Departments of Agriculture and Health and Human Services. This table has a wide range for what the pamphlet calls "healthy" or "suggested" weights. In this table, the higher weights generally apply to men, who tend to have more muscle and bone. The lower weights more often apply to women, who have less muscle and bone. The table also shows higher weights for people age 35 and older, which some expert question.



2.2 Body Mass Index (BMI)

Body mass index, or BMI, is a new term to most people. However, it is the measurement of choice for many physicians and researchers studying obesity. BMI uses a mathematical formula that takes into account both a person's height and weight. BMI equals a person's weight in kilograms divided by height in meters squared. (BMI = kg/m2).

The table printed here has already done the math and metric conversions. To use the table, find the appropriate height in the left-hand column. Move across the row to the given weight. The number at the top of the column is the BMI for that height and weight **(O'Rahilly and Farooqi, 2006)**.

In general, a person age 35 or older is obese if he or she has a BMI of 27 or more. For people age 34 or younger, a BMI of 25 or more indicates obesity. A BMI of more than 30 usually is considered a sign of moderate to severe obesity.

The BMI measurement poses some of the same problems as the weight-for-height tables. Doctors don't agree on the cutoff points for "healthy" versus "unhealthy" BMI ranges. BMI also does not provide information on a person's percentage of body fat. However, like the weight-for-height table, BMI is a useful general guideline.

TABLE I

Body Weights in Pounds According to Height and Body Mass Index*

* Each entry gives the body weight in pounds (lbs.) for a person of a given height and body mass index. Pounds have been rounded off. To use the table, find the appropriate height in the left-hand column. Move across the row to a given weight. The number at the top of the column is the body mass index for the height and weight.

Body Mass Index (kg/m²)														
	19	20	21	22	23	24	25	26	27	28	29	30	35	40
Ht. (in.)	*Body Weight (lbs.)*													
58	91	96	100	105	110	115	119	124	129	134	138	143	167	191
59	94	99	104	109	114	119	124	128	133	138	143	148	173	198
60	97	102	107	112	118	123	128	133	138	143	148	153	179	204
61	100	106	111	116	122	127	132	137	143	148	153	158	185	211
62	104	109	115	120	126	131	136	142	147	153	158	164	191	218
63	107	113	118	124	130	135	141	146	152	158	163	169	197	225
64	110	116	122	128	134	140	145	151	157	163	169	174	204	232
65	114	120	126	132	138	144	150	156	162	168	174	180	210	240
66	118	124	130	136	142	148	155	161	167	173	179	186	216	247
67	121	127	134	140	146	153	159	166	172	178	185	191	223	255
68	125	131	138	144	151	158	164	171	177	184	190	197	230	262
69	128	135	142	149	155	162	169	176	182	189	196	203	236	270
70	132	139	146	153	160	167	174	181	188	195	202	207	243	278
71	136	143	150	157	165	172	179	186	193	200	208	215	250	286
72	140	147	154	162	169	177	184	191	199	206	213	221	258	294
73	144	151	159	166	174	182	189	197	204	212	219	227	265	302
74	148	155	163	171	179	186	194	202	210	218	225	233	272	311
75	152	160	168	176	184	192	200	208	216	224	232	240	279	319
76	156	164	172	180	189	197	205	213	221	230	238	246	287	328

Adapted with permission from Bray, G.A., Gray, D.S. Obesity. Part I. Pathogenesis. West J. Med. 1988; 149:429–41.

2.3 Waist-to-Hip Ratio

It is a simple way to measure whether someone is an apple or a pear, because doctors are concerned with not only how much fat a person has but where the fat is on the body. People whose fat is concentrated mostly in the abdomen are more likely to develop many of the health problems associated with obesity.

To find out someone's waist-to-hip ratio, measure the waist at its narrowest point, and then measure the hips at the widest point. Divide the waist measurement by the hip measurement. A woman with a 35-inch waist and 46-inch hips would do the following calculation:

35 ÷ 46 = 0.76

Women with waist-to-hip ratios of more than 0.8 or men with waist-to-hip ratios of more than 1.0 are "apples." They are at increased health risk because of their fat distribution.

3. Physiological basis of obesity

Obesity is caused by perturbations of the balance between food intake and energy expenditure, which is regulated by a complex physiological system that requires the integration of several peripheral signals and central coordination in the brain **(Bell *et al.*, 2005; Timper, and Brüning, 2017).**

The hypothalamus functions as a central regulator in this system. It receives information about energy balance through neuronal and hormonal signals to several tissue nuclei within it —particularly the ventro-medial, paraventricular and arcuate nuclei — and to the lateral hypothalamic area **(Fig. 1)**.

The arcuate nucleus has an essential role in this system; it contains two sets of neurons, **one** produces agouti-related protein **(AGRP)** and neuropeptide Y **(NPY)** and the other produces pro-opiomelanocortin **(POMC)** and cocaine- and amphetamine-related transcript **(CART)**. The first type are orexigenic, promoting food intake and reducing energy expenditure, and the second type produce the opposite anorexigenic effect **(Brash *et al.*, 2002),** and exerts its effects by signalling to various downstream effector neurons as shown in **Fig. 1**.

Analysis of these physiological pathways has highlighted possible candidate genes that might underlie the genetic basis of obesity. In turn, genetic studies have contributed significantly to understanding the physiology of weight regulation, through both the use of animal models and the investigation of the genetics of rare and common human forms of obesity.

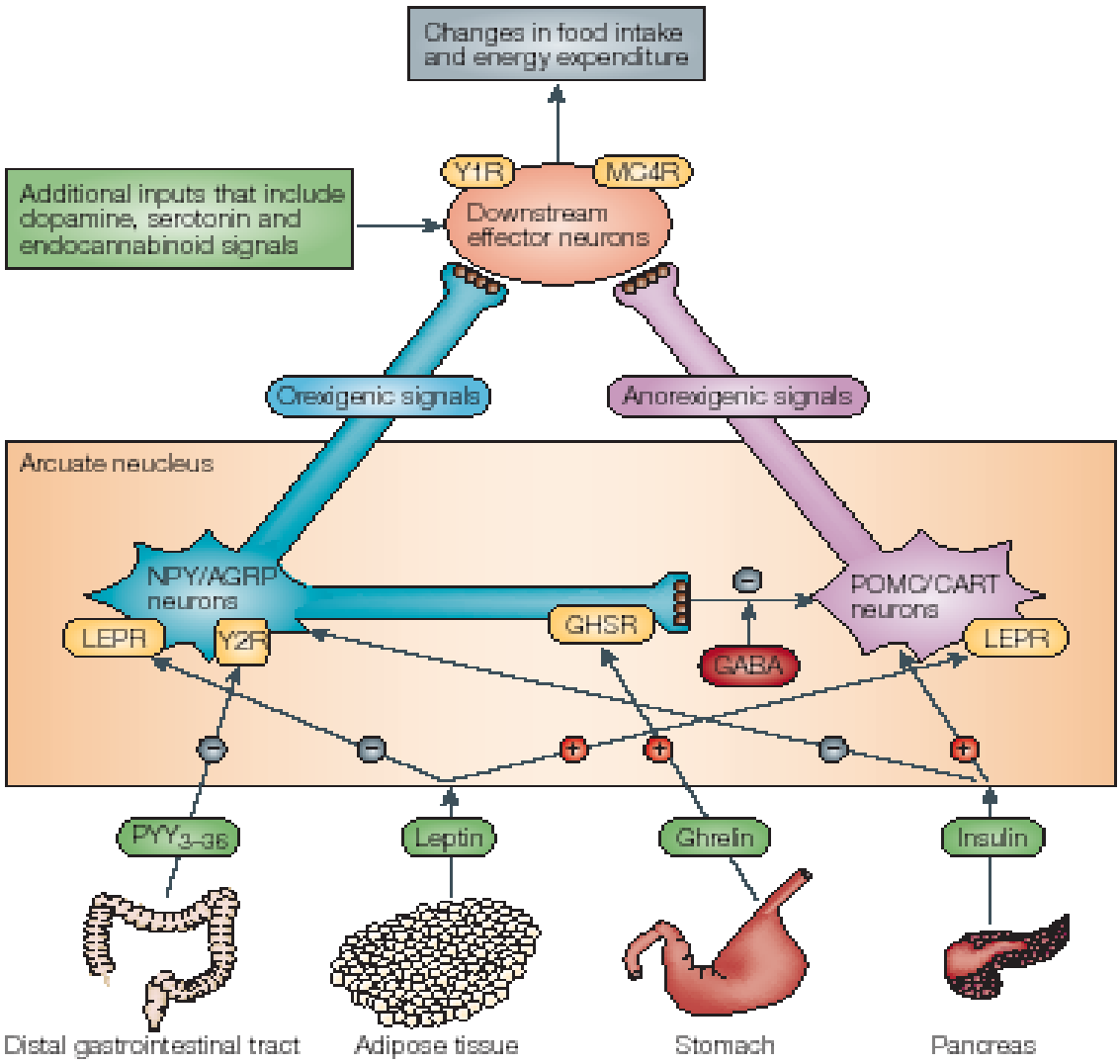


Fig 1: Physiological regulation of energy balance. The neuropeptide Y (NPY)/agouti-related protein (AGRP) neurons, and the pro-opiomelanocortin (POMC)/ cocaine and amphetamine related transcript (CART) neurons in the arcuate nucleus of the hypothalamus have key roles in the regulation of energy balance. Activation of the NPY/AGRP neurons has an orexigenic effect, promoting food intake, whereas the POMC/CART neurons have the opposite anorexigenic effect. These two sets of neurons receive input from several endocrine hormones, including leptin, insulin, and ghrelin.

4. Causes of obesity

In scientific terms, obesity occurs when a person's calorie intake exceeds the amount of energy burned. Causes of this imbalance are still unclear. Evidence suggests that obesity often has more than one cause. **Genetic, environmental, psychological, and other factors** all may play a part.

4.1 Genetics Factors

The recent and relatively rapid rise in the prevalence of obesity in the last 30 years has led some to question the importance of genetics in the aetiology of obesity. It tends to run in families, suggesting that it may have a genetic cause. However, family members share **not only genes** but also **diet** and **lifestyle habits** that may contribute to obesity. Separating these lifestyle factors from genetic ones is often difficult. Still, growing evidence points to heredity as a strong determining factor of obesity **(O'Rahilly and Farooqi, 2006; Hruby and Hu, 2015.).**

In one study of adults who were adopted as children, researchers found that the subjects' adult weights were closer to their biological parents' weights than their adoptive parents'. The environment provided by the adoptive family apparently had less influence on the development of obesity than the person's genetic makeup.

Nevertheless, people who feel that their genes have doomed them to a lifetime of obesity should take heart. Many people genetically predisposed to obesity do not become obese or manage to lose weight and keep it off **(Mhtml:file://F:\OBESITY\Genetic%20Obesity.mht)**.

4.2 Environmental Factors:

Although genes are an important factor in many cases of obesity and genetics can indicate a predisposition to obesity, Obesity genetics cannot be singled out as the only cause of the obesity epidemic. Since, researchers have found that a person's environment includes lifestyle behaviors also plays a significant part. Parents who are overweight and do not exercise are likely to pass those habits on to their children. It is therefore important for adults to take control of their health and set the right example **(Mhtml:file://F:\OBESITY\Genetics%20 obesity 1.mht)**.

People can't change their genetic makeup, of course, but they can change what they eat and how active they are. Some people have been able to lose weight and keep it off by:

- learning how to choose more nutritious meals that are lower in fat.
- learning to recognize environmental cues (such as enticing smells) that may make them want to eat when they are not hungry.
- Becoming more physically active.

4.3 Psychological Factors

Psychological factors also may influence eating habits. Many people eat in response to

negative emotions such as boredom, sadness, or anger. While most overweight people have no more psychological disturbance than normal weight people, about 30 percent of the people who seek treatment for serious weight problems have difficulties with binge eating. During a binge eating episode, people eat large amounts of food while feeling they can't control how much they are eating. Those with the most severe binge eating problems are considered to have **binge eating disorder(Mhtml:file://F:\OBESITY\Genetic%20 Obesity.mht)**.

These people may have more difficulty losing weight and keeping the weight off than people without binge eating problems. Some will need special help, such as counseling or medication, to control their binge eating before they can successfully manage their weight.

4.4 Other Causes of obesity

Some rare illnesses can cause obesity. These include **hypothyroidism**, **Cushing's syndrome**, **depression,** and **certain neurologic** problems that can lead to overeating. Certain **drugs**, such as **steroids** and **some antidepressants**, may cause excessive weight gain. A doctor can determine if a patient has any of these conditions, which are believed to be responsible for only about 1 percent of all cases of obesity.

5. HERITABILITY OF BODY WEIGHT

The heritability of a trait is defined as the per cent of inter-individual variation in that trait that can be explained by inherited factors. When considering obesity, clearly heritability is not a fixed entity, as the proportion of the phenotype that can be explained by the genotype will be influenced by the varying exposure to obesogenic environmental factors in different individuals and families.

The comparison of monozygotic and dizygotic twin pairs has traditionally been one of the most powerful ways of obtaining a reliable estimate of heritability. Heritability estimates for obesity related phenotypes varied from 6% to 85% among various populations **(Yang *et al*., 2007; Dubois et al., 2012)**. In the case of BMI there have been over 30 published studies **(Maes et al. 1997)**, and the estimated heritability of BMI ranges between 64 and 84% **(Stunkard et al. 1986)**.

It has long been considered that genetic variation between individuals is likely to influence responses to environmental factors such as diet and levels of physical activity.

That means when food intake and exercise are controlled, inherited factors influencing either energy expenditure or nutrient partitioning has an important influence on weight gain. Similar data was obtained by the same group when inducing negative energy balance in identical twin pairs **(O'Rahilly and Farooqi, 2006)**.

6. Genetics of obesity

Research has shown that genetics can affect obesity in many ways. Some factors that are

influenced by genes, and may cause or perpetuate obesity, including:

1-appetite level and sense of fullness

2-calories burned during exercise.

3-calories burned while resting.

In addition, how the body handles excess fat, and where it is stored, may be the result of genetics. Even on a low-calorie diet, some people have trouble losing or maintaining weight. Others may go through vigorous exercise programs with slower-than-normal results. These factors may be part of your body and cell structure **(Mhtml:file://F:\OBESITY\Genetics%20obesity 1.mht)**.

6.1 Studies in obesity genetics

Studies conducted in adoptee households confirm the genetics of obesity. Upon reaching adulthood, adopted children tend to reflect the bodily features of their birth parents. Identical twins who have been raised apart also reflect these same patterns. This suggests that genetics does play a large role in a person's weight.

Studies continue to link gene mutations with obesity. For instance, some individuals are morbidly obese from infancy. This is rare, but may be a broad indicator of specific problems in gene structure. One such report found that **leptin**, a hormone responsible for regulating appetite, was defective. Other damaged **appetite controllers** appear to be in the form of **PCI**, an enzyme. Experts also cite a link between obesity and the **FTO gene**, which is linked to fat buildup **(Mhtml:file://F:\OBESITY\Genetics%20obesity 1.mht)**.

Researchers often refer to **polymorphisms**, which are the small differences in genes affecting one percent or more of a given group. Studies continue to uncover new genetic links that provide possible explanations for how we gain and lose weight. While polymorphisms only affect a small percentage of the population, finding them is helpful in creating new ways to treat obesity.

Recently, single nucleotide polymorphisms (SNPs) in proopiomelanocortin, a precursor peptide, have been found to associate with obesity-related variables in a Hispanic population **(Sutton *et al*., 2005; Gao et al., 2019)**. Thus, as is the case with common forms of type 2 diabetes, it does appear that subtle variants in genes, which when mutated result in severe early onset obesity, are likely to contribute to susceptibility to obesity in the general population.

New evidence that genetics plays a key role in obesity is published in the ***International Journal of Bioinformatics Research and Applications***. The findings relate to the genetics of modern Pima Indians who have an unusually high rate of obesity but could be extrapolated to all people. Their obesity is thought to be linked to a thrifty metabolism that allowed them to metabolize food more efficiently in times when little was available but causes problems when food is in abundance.

Research based on the **"thrifty gene"** hypothesis is frequently cited in quotes on obesity and genetics. **James Neel,** a geneticist, first proposed this theory in **1962**. The "**thrifty gene**" hypothesis suggests that our genes follow the ancestral pattern of "feast or famine." In other words, our bodies store fat when food is plentiful in preparation for leaner times. In today's society, the feast continues without the famine, leading to weight gain **(Chakravarthy and Booth, 2003)**.

Moreover, some studies have focused upon inheritance patterns without focusing upon specific genes. One study found that 80% of the offspring of two obese parents were obese, in contrast to less than 10% of the offspring of two parents who were of normal weight **(Kolata and Gina, 2007; Hieronimus and Ensenauer, 2021)**.

Genetic studies have shown that the particular set of weight-regulating genes that a person has is by far the most important factor in determining how much that person will weigh. The heritability of obesity—a measure of how much obesity is due to genes versus other factors—is about the same as the heritability of height. It's even greater than that for many conditions that people accept as having a genetic basis, including heart disease, breast cancer, and schizophrenia **(mhtml:file://F:\OBESITY\Obesity%20is%20Genetic%20-%20Newsweek com.mht)**.

There are different forms of obesity that have been identified with respect to the causes of obesity, either mutation in single gene, environmental factors or both of them. These obesity forms including: monogenic, syndromic and polygenic forms of obesity.

Monogenic forms of obesity

Some forms of obesity are caused by mutations in single genes. These forms of obesity are rare and very severe, generally starting in childhood **(Farooqi and Rahilly 2004; Thaker, 2017).** Currently 176 human obesity cases due to single gene mutations in 11 different genes have been reported **(Yang *et al*. 2007)**, including the **leptin, leptin receptor, proopiomelanocortin (POMC)** and the **melanocortin four receptor genes (MC4R)**.

MC4R is the most frequent autosomal dominant form of obesity which is caused by mutations in the gene that encodes MC4R. It represents the most common monogenic obesity disorder present in 1-6% of obese individuals from different ethnic groups **(Bell *et al*. 2005)**. Till date, 50 loci related to Mendelian syndromes relevant to human obesity have been mapped to a genomic region and causal genes or strong candidates have been identified for most of the syndromes **(Rankinen *et al*. 2006)**.

Syndromic Forms of Obesity

At least 20 rare syndromes due to discrete genetic defects or chromosomal abnormalities, both autosomal and X-linked, are characterized by obesity, such as **Prader-Willi syndrome,**

Bardet-Biedl syndrome, Cohen syndrome, Ayazi syndrome, and **MOMO syndrome**. (The term "non-syndromic obesity" is sometimes used to exclude these conditions.) **(Walley *et al*., 2009)**. In people with early-onset severe obesity (defined by an onset before 10 years of age and body mass index over three standard deviations above normal), 7% harbor a single locus mutation **(Farooqi and O'Rahilly, 2006)**.

***i*-Prader-Willi syndrome**: PWS

The Prader–Willi syndrome (PWS) is an autosomal dominant disorder characterized by hypotonia, mental retardation, short stature, hypogonadotropic hypogonadism and hyperphagia a. It is characterized by obesity and caused by a paternally inherited deletion at the chromosomal region **15q11.2 – q12** and less frequently by maternal uniparental disomy **(Bell *et al.* 2005)**. Molecular causes that underlie the etiology of syndromic obesity are more complex than for monogenic cases and further studies are necessary to reveal their genetic basis as shown in **Fig 2**.

There is a lack of expression of paternally imprinted genes within the 4.5 Mb PWS region and several candidate genes have been studied and their expression shown to be absent in the brains of PWS patients **(Swaab *et al*. 1995)**. However, the precise role of these genes and the mechanisms by which they lead to a pleiotropic obesity syndrome remain elusive.

***ii*- BARDET–BIEDL SYNDROME:** BBS

BBS is autosomal recessive disease characterized by obesity, mental retardation, dysphormic extremities (syndactyly, brachydactyly or polydactyly), retinal dystrophy or pigmentary retinopathy, hypogonadism and structural abnormalities of the kidney or functional renal impairment **(Katsanis *et al*. 2001)**.

BBS is a genetically heterogeneous disorder that is now known to map to at least eight loci: 11q13 (BBS1), 16q21 (BBS2), 3p13–p12 (BBS), 15q22.3–q23 (BBS4), 2q31 (BBS5), 20p12 (BBS6), 4q27 (BBS7) and 14q32.11 (BBS8) as shown in **(Mykytyn *et al*. 2004)** human obesity gene map **(Fig. 3)**. Mice lacking the BBs4 protein recapitulate the major components of the human phenotype, including obesity and retinal degeneration **(O'Rahilly and Farooqi 2006)**. The genetic basis of BBS is typically autosomal recessive; however, the occurrence of triallelic inheritance has been suggested in some families.

Polygenic forms of obesity

The more common forms of obesity must be considered as a complex polygenic disease involving both gene-gene and gene-environment interactions. However, unlike the monogenic obesity, identification of specific susceptible genes is difficult. Currently over 430 genes or chromosomal regions have been implicated in the etiology of obesity **(Nirmala *et al*., 2008)**.

It is clear from the twin, adoption and family studies that obesity in highly heritable and an individual's risk of obesity increases when one has relatives who are obese. The association between various environmental factors, such as body mass index, energy intake, fat mass, adipose tissue metabolism and genes for obesity development **(Fig. 4)** has been evidenced **(Nirmala *et al*., 2008)**.

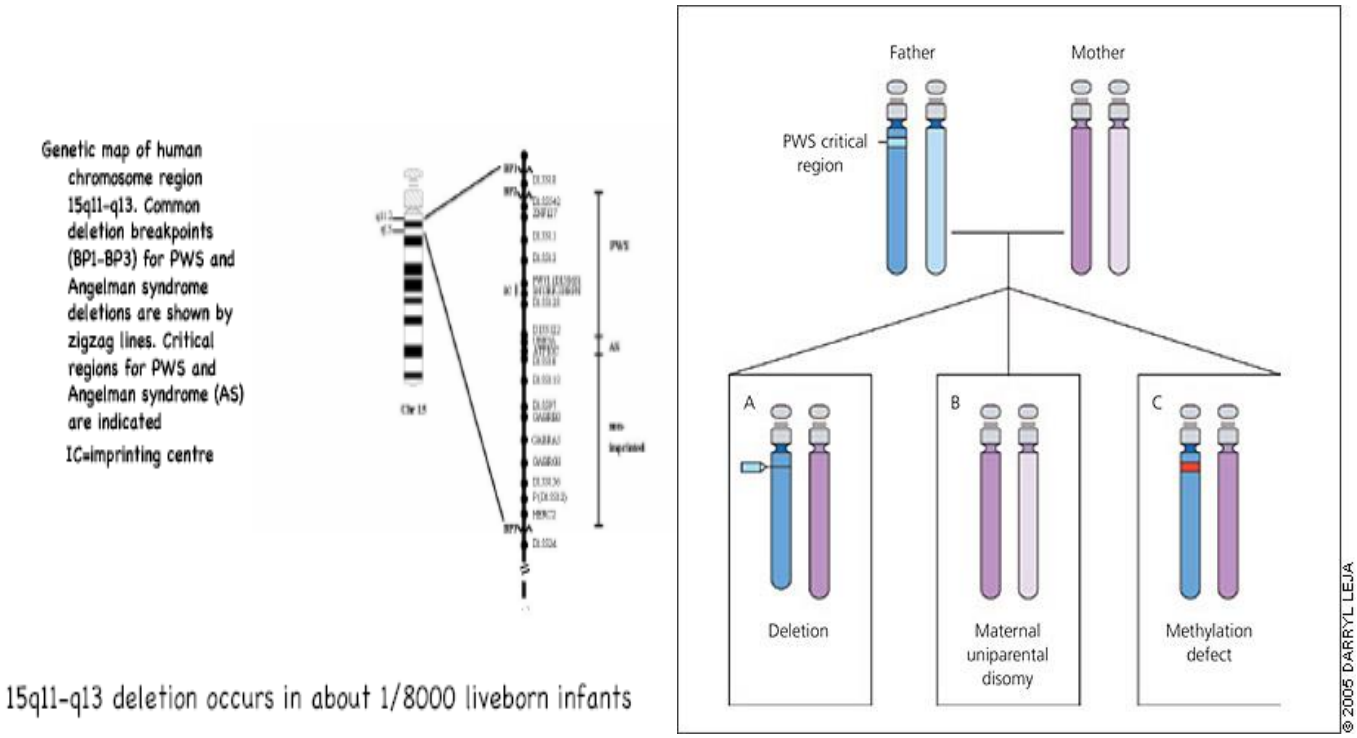


Fig. 2: Showing Prader Willi syndrome (PWS) gene map (Left side) and causes of PWS syndrome either inherited deletion or maternal disomy (Right side).

6.2 Approaches for identifying obesity genes

Two approaches that are commonly used across the whole field of complex human genetics have been used to identify the underlying genes: **candidate-gene** and **whole-genome** approaches.

***i*- Candidate-gene studies**

The design of the candidate gene approach is simple; including the identification of a gene that is involved in the disease phenotype, a polymorphic marker within that gene and a suitable set of subjects to genotype for that marker. There are **two main types** of candidate genes that are generally considered in such studies: **functional** and **positional**.

Functional candidates are genes with products that are in some way involved in the pathogenesis of the disease. Clearly, this is highly dependent on the current state of knowledge about a disease, in obesity; they are involved in the regulation of energy metabolism, appetite control or autocrine–paracrine signaling by adipocytes. The identification of signaling molecules such as

leptin and **POMC** has provided a great stimulus to the field. A possible role of less deleterious variants of genes that are responsible for monogenic forms of obesity has been proposed for common obesity. Whereas, **positional candidates** are genes identified because they lie within regions of the genome that have been shown to be genetically important in association or association studies, or through the discovery of chromosomal translocations that disrupt the gene.

Obesity is so heterogeneous in human populations that meta-analyses of genetic studies for obesity can be difficult to evaluate due to the widely differing obesogenic environments that subjects are recruited from. The way forward now is to investigate the functional roles of the current candidate genes in model organisms and *in vitro* cell systems. This will allow the development of functional assays that can then be used to test putative activator or inhibitor molecules as possible therapeutic agents.

***ii*- Genome-wide linkage studies**

This is a useful approach as, unlike the candidate-gene studies described above, it does not rely on any pre-existing knowledge of the genes that underlie the trait being studied. There has been success using this method in complex traits, e.g. obesity **(Nirmala *et al*., 2008; van Dijk et al., 2015).** Human obesity is a complex trait found to be determined by the interaction of multiple genes and environmental factors. **Genome wide linkage** scans exploit familial relationship and rely on use of highly polymorphic markers that spread across the whole genome to pinpoint the location of genes, followed by calculating the degree of linkage of the marker to a disease trait **(Nirmala *et al*., 2008; Hoffmann et al., 2018)**.

For obesity, **genome wide scans** have been performed in two kinds of samples: (1) Families from the general population (2) Families that include one obese proband. For quantitative trait analysis, large families from a general population with high prevalence of obesity are required **(Bell et al., 2005)**. In fact, the first genome wide scan using this method for obesity phenotype was reported by **Comuzzie *et al*. (1997)**. They studied Mexican American families from the San Antonio Family Heart Study for leptin levels and fat mass at 2p21. The first genome wide analysis using nuclear families ascertained specifically for obesity also found a locus for obesity at 2p21 and another at 10p12 **(Hager *et al*. 1998).**

Subsequently, many loci have been identified with the evidence of linkage with numerous obesity related phenotypes including body mass index, waist circumference, and body fat. Linkage of body mass index to almost every chromosomal region except Y was reported by many genome wide linkage studies. The most promising genetic regions in chromosomes 2, 3, 6, 11, 13 and 20 were replicated in many studies with reference to body mass index **(Yang *et al*. 2007)**.

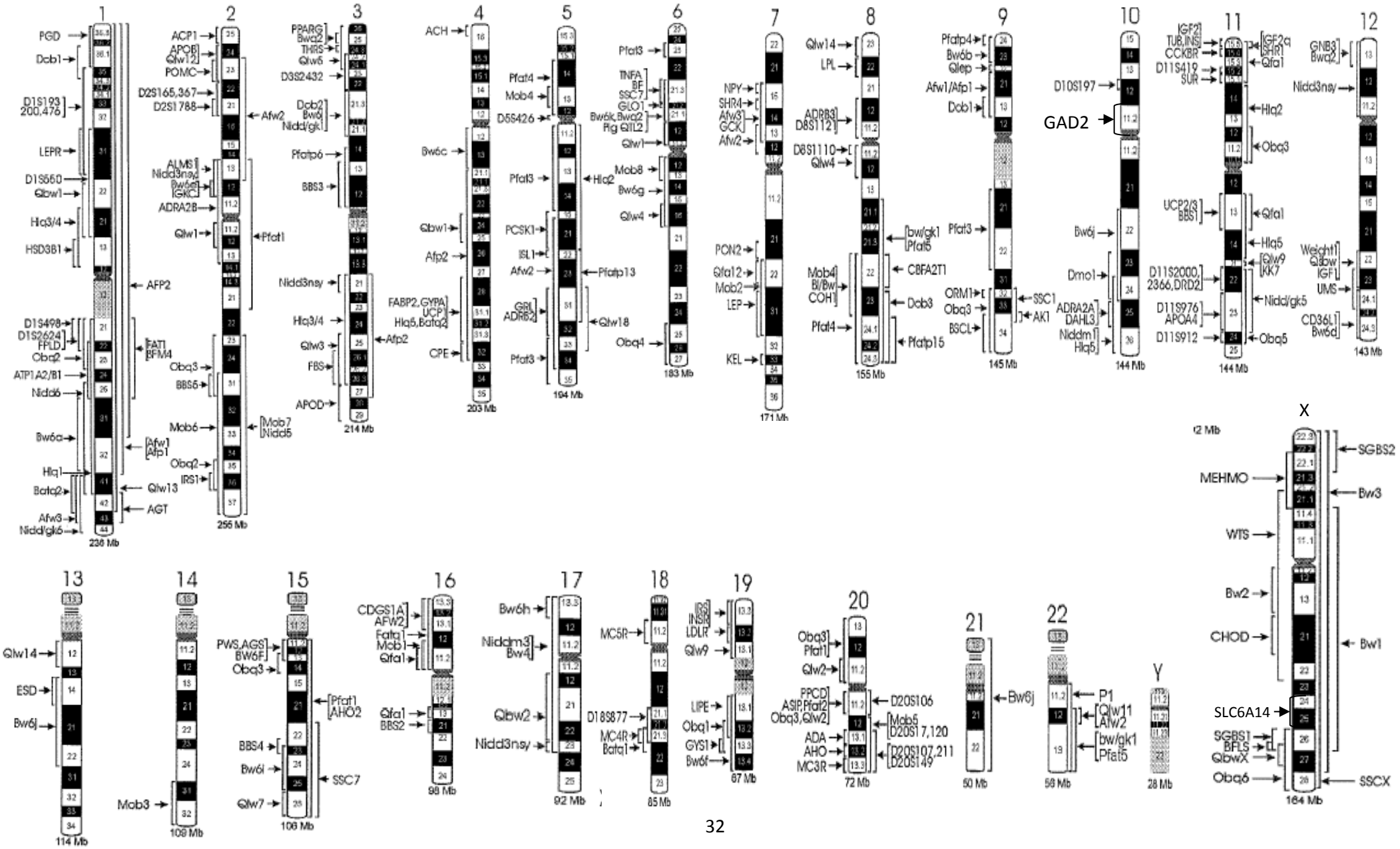


Fig. 3: Human obesity gene map

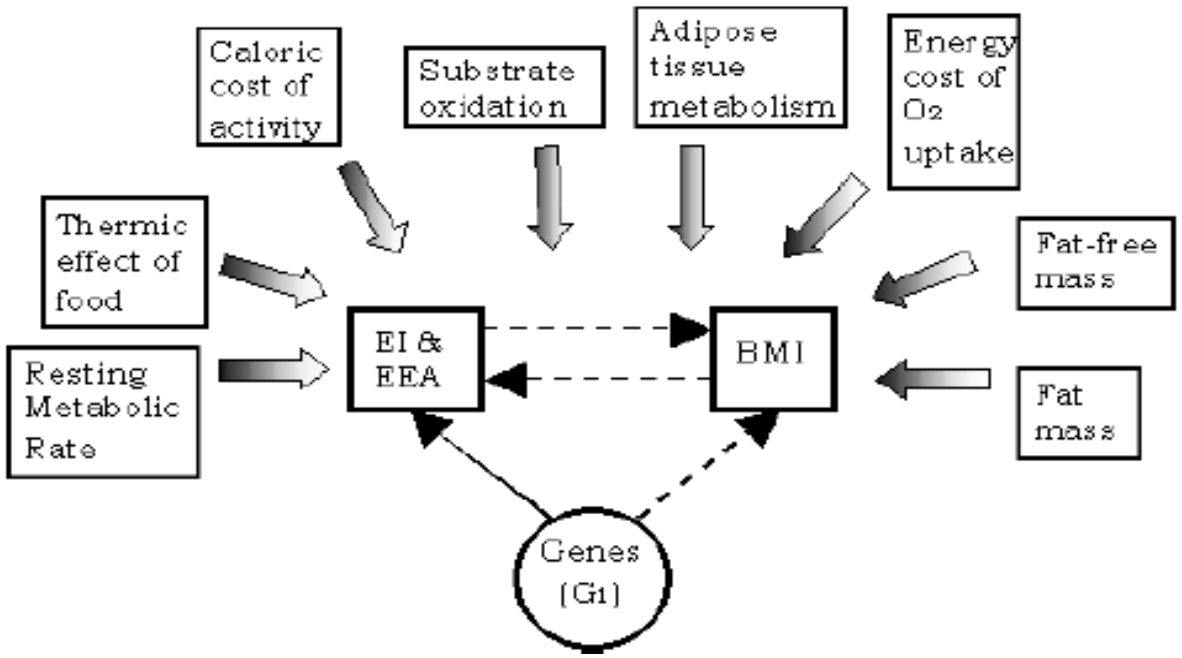


Fig. 4: Schematic representation of the factors that underlie the association between Body Mass Index (BMI), Energy Expenditure at Activity (EEA), Energy Intake (EI). Genes (G1; in the circle) is a hypothetical familial factor (one or more major genes and/or polygenetic effects) that underlies each of the energy and BMI traits (squares). Dashed line indicates direct effect. Additional factors that may impact on the energy balance-BMI relationship are shown in the top portion of the figure.

***6.3* Genes responsible for obesity**

Obesity is a complex non-mendelian trait and may depend on several susceptible genes with low or moderate effects. **Loktionov (2003)** stated firm evidence on the influence of genes in energy homeostasis and thermogenesis adipogenesis leptin-insulin signaling transduction and hormonal signaling peptide to play a role in the development of obesity.

The discovery of a gene that influences the development of obesity in the general population provides a new tool for understanding how some people appear to gain weight more easily than others**.** Over the past decade, scientists have identified many of the genes that regulate body weight and have proved that in some instances, different variants of these genes can lead a person to be fat or thin. These genes underlie a weight-regulating system that is remarkably precise.

Polymorphisms in various genes controlling appetite and metabolism predispose to obesity when sufficient calories are present. The percentage of obesity that can be attributed to genetics varies depending on the population examined from 6% to 85% **(Yang *et al.*, 2007; Thaker, 2017)**.

Many studies reported association between DNA sequence variation in specific genes and

obesity phenotypes **(Rankinen *et al.*, 2006; Thaker, 2017).** So far, 426 findings of positive associations in 127 genes have been reported. Among them, 22 genes are prominent and each supported by at least five positive studies, while 12 of those are supported by at least 10 positive replication studies **(Nirmala *et al.*, 2008)**. This suggests that as many as 20% to 30% of the obesity candidate genes identified might contribute to the risk of obesity in humans.

Energy storage in the form of fat is an important adaptation for survival. Thus, it is likely that combination of genes have been selected during evolution to favor energy storage (the "thrifty gene" hypothesis) **(Spiegelman and Flier, 2001)**. In our context of increased food availability and decreased physical activity, these genes will confer a susceptibility to the development of obesity and its maintenance.

As previous shown, a number of genes have been linked to obesity in the biomedical literature **(Snyder *et al.*, 2004)**. However, it is not as simple as there being a "fat" gene or a"skinny" gene. Instead there is a complex relationship between neurotransmitters in the brain, genes, and obesity. Neurotransmitters, including dopamine and serotonin, regulate food intake, and are thus related to obesity **(Guo *et al.*, 2006)**. Hence, the genetic defects found to date all impair satiety, affecting the function of appetite control centres in the brain rather than being due to a 'slow metabolism'**(Farooqi and O'Rahilly, 2005)**. Certain genes interact with these neurotransmitters. Furthermore, the interaction depends on the exact genotype, with certain polymorphisms of genes related to high obesity and others to low obesity, some of these genes are discussed in detail in the following points:

***i*- GAD2 as a candidate gene for obesity**

GAD2 is a positional candidate gene, identified in French Caucasians, located at 10p11.23 as shown in human obesity gene map **(Fig. 3)**. It is identified in 575 cases, characterized by morbid obesity and eating behaviors **(Pe´russe *et al.*, 2005)**.

It encodes the glutamic acid decarboxylase enzyme GAD65, which is involved in the formation of γ-aminobutyric acid (GABA) from L-glutamic acid. GABA functions together with the neuropeptide Y in the paraventricular nucleus to increase **(Bell *et al.*, 2005)** food intake as shown in Fig. 5

and disinhibition for food intake. In addition, in children, GAD2 SNPs are associated with obesity in which there is an increased risk for 'binge eating' behavior, especially in girls **(Meyre *et al.* 2005)**.

Polymorphisms in **GAD2 might** affect the GAD65 enzyme and so result in the increased production of GABA, which has a significant orexigenic role. In adults, the *GAD2* –243A>G SNP is associated with higher scores for hunger

Although GAD2 SNPs cannot account for all of the linkage to the 10p region, these data highlight the importance of the GABA-related pathways in the regulation of food intake in humans. Genes that are involved in the GABA- and glutamate signaling pathways, including those that encode the receptors and transporters of these molecules, are therefore among the potential candidates for polygenic obesity. The linkage peak and gene diagram are modified from **(Bell *et al.*, 2005)**.

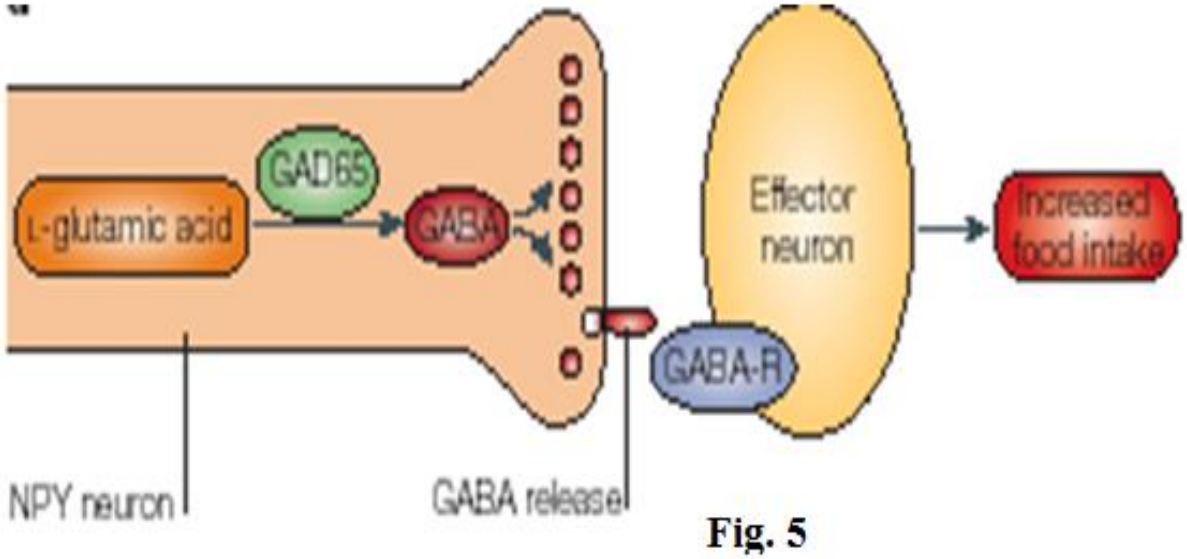


Fig. 5

***ii*- The SLC6A14 candidate gene**

SLC6A14 gene is a positional candidate gene, identified in a genome-scan of a Finnish population, located at Xq23-q24 (Fig. 3) of 1267 cases characterized by Obesity and eating behaviors **(Bell *et al.*, 2005)**. Since, analysis of candidate genes in a case-control study detected a significant association of variants in the solute carrier family 6 member 14 gene with obesity, hence its derived name SLC6A14 gene.

The *SLC6A14* gene encodes a sodium- and chloride-dependent transporter of neutral and cationic amino acids that has a high affinity for the non-polar amino acid tryptophan. In the brain, the enzyme tryptophan hydroxylase converts tryptophan into serotonin (5-hydroxytryptamine (5-HT)) **(Fig. 6)**.

This neurotransmitter is known to be strongly involved with the central signalling of satiety by mechanisms that include effects on downstream effector neurons in the hypothalamus **(Fig. 1)**. Therefore, a possible hypothesis is that a reduction in the concentration of serotonin owing to reduced tryptophan transport might be the link with lower *SLC6A14* activity, and thereby increasing susceptibility to obesity by reducing satiety **(Bell *et al.*, 2005)**.

Recently, the association between the same *SLC6A14* SNPs and obesity was confirmed in a study in a French population where they were also found to modulate hunger and satiety scores. Variants that affect non-coding regions can have many unpredictable effects, which can be difficult to determine, and no functional studies have been reported for these *SCL6A14* variants so far **(Bell *et al*., 2005)**.

***iii*- Leptin and leptin receptor genes**

A gene designated as ob (for obese) was identified. The ob gene product is a protein called leptin from the Greek word leptos, **meaning thin**. The gene has been designated **LEP gene**. Recently LEP gene is localized at (7q31.3 and 7q32) long arm of human chromosome number 7 **(Pe´ russe *et al*., 2005)** as shown in human obesity gene map **(Fig. 3)**.

In humans, circulating leptin concentrations are highly correlated with both body mass index and percent body fat. Similar relationships were described between a variant in the exon 1 noncoding region and circulating leptin levels in French obese adults. These studies suggest that genetic variation in the leptin gene may account for the variation in circulating leptin levels and thus could modify the ability of the brain to sense the amount of fat stored in white adipose tissue **(Clement and Ferre, 2003).**

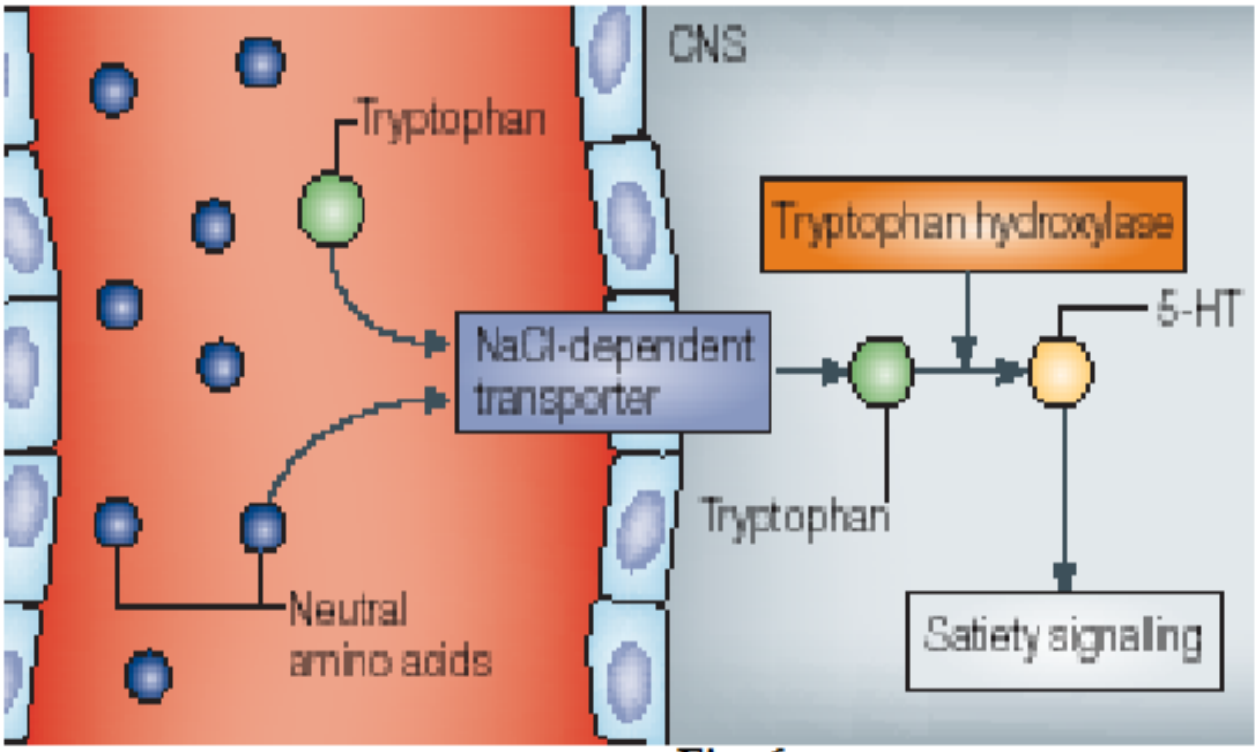


Fig. 6

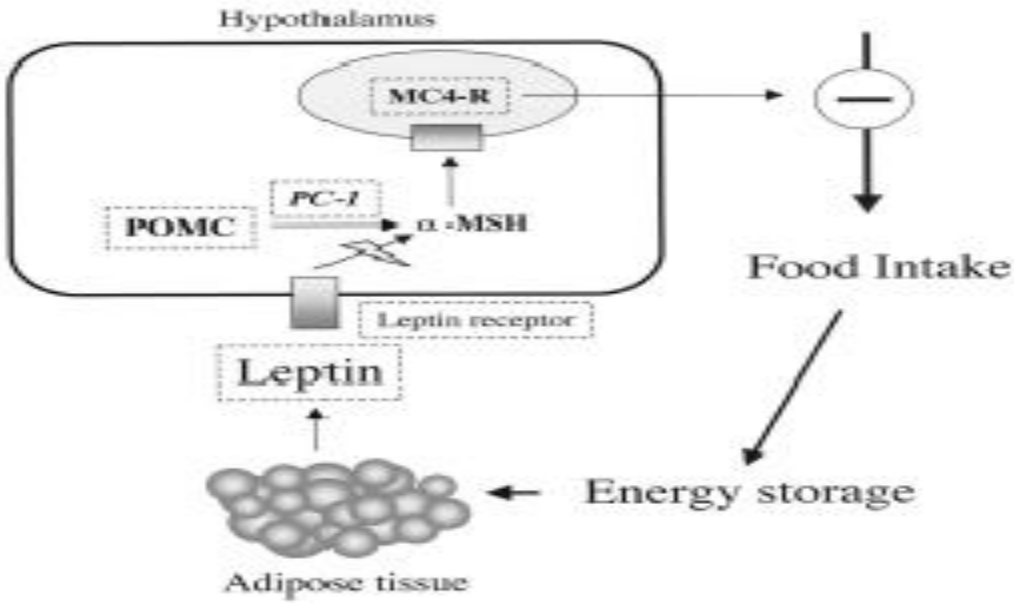


Fig. 7: Schematic representation of leptin regulation of food intake and proteins mutated in human obesities.

Leptin is a cytokine-like polypeptide produced by the adipocyte that controls food intake through the activation of hypothalamic receptors. Leptin is secreted by adipocytes. It binds to hypothalamic receptors in the arcuate nucleus and this induces, among other effects, an increased synthesis and secretion of α-melanocyte stimulating hormone (α-MSH.). α-MSH is formed from pro-opiomelanocortin (POMC) through proteolytic cleavage mediated by pro-hormone convertase 1 (PC-1). α-MSH binds to the melanocortin 4 receptor (MC4R) in the paraventricular nucleus. This, in turn, inhibits the effectors of food intake **(Clement and Ferre, 2003)** as shown in previous **(Fig. 7)**; mutated steps that have been identified in human monogenic forms of obesity are circled with a *dotted line*.

Leptin is produced proportionally to the adipose mass and thus informs the brain of the fat store level. It also decreases the expression of orexic peptides such as neuropeptide Y. Other hormones, ghrelin (orexic), insulin (anorexic), and cholecystokinin (anorexic), are involved in the short-term control of energy intake. If a large amount of leptin is produced, the hypothalamus reacts by reducing appetite and accelerating the body's metabolism. But if the ob gene is defective and the amount of leptin is reduced, the hypothalamus might be induced to continually

signal a need for food **(Bray, 1997; Clement and Ferre, 2003)**.

Homozygous carriers of a loss-of-function mutation in the leptin gene display morbid obesity with onset in the first months of life, hypogonadism and central hypothyroidism. **(Barsh *et al*., 2000)**. Affected subjects continuously seek food and eat considerably more than their siblings. In one case, a leptin-deficient child has been treated by leptin replacement.

Leptin receptor gene is designed as LEPR gene, located at the short arm (1p31) of human chromosome number one **(Fig. 3)**. LEPR mutation abolishes leptin signaling, leading to a phenotype similar to that of individuals with leptin deficiency. However, it is more severe than LEP gene mutations **(Clement and Ferre, 2003)**.

***iv*- Pro-opiomelanocortin (POMC) gene**

The POMC gene, a plausible candidate for polygenic obesity, encodes POMC protein. It is present in one locus and linked with obesity in genome-wide scan analysis. One study describes higher leptin levels in Italian obese children with a mutation in POMC gene **(Del Giudice *et al*., 2001)**. It is located at short arm (2p23.3) of human chromosome number two as shown in human obesity gene map **(Fig. 3)**.

POMC is a peptide expressed in human brain, gut, placenta, and pancreas. It is the precursor of many hormones, including ACTH and α-MSH produced by PC-1-dependent cleavage. As shown in Fig. 7 **(Clement and Ferre, 2003)**.

Phenotype associated with a defect in POMC function include obesity, altered pigmentation, and ACTH deficiency, since, α-MSH is involved in the regulation of food intake and also in hair pigmentation. Two children with homozygous or compound heterozygous loss-of-function mutations in POMC exhibited a phenotype including obesity, red hair, and adrenal insufficiency, reflecting the lack of pituitary neuropeptides derived from the POMC gene **(Krude and Gruters, 2000)**.

Mutations of PC-1 have also been described and are associated with obesity and ACTH insufficiency, as for POMC mutations. However, these subjects also demonstrate hyperproinsulinemia, because PC-1 is involved in the conversion of proinsulin into insulin in the pancreatic β-cell **(Brash *et al*., 2000)**.

***v*- Melanocortin 4 receptor (MC4R) gene**

MC4R gene encodes melanocortin 4 receptor that is the receptor of α-MSH (Fig. 7). According to human obesity gene map, MC4R is located at long (18q22) arm of chromosome number 18 (Fig). Mutations in the MC4R cause dominant and recessive inherited nonsyndromic obesity **(Clement and Ferre, 2003)**.

In patients with MC4R mutations, the frequency and relative risk for obesity (100-fold higher) could lead us to consider mutation screening at a population scale. Human obesity

caused by MC4R mutations is similar to more common forms of obesity, with an earlier age of onset. Interestingly, a trend toward a greater incidence of childhood obesity and an excessive hunger and food-seeking behavior from the age of 6 to 8 months has been reported **(Brash *et al*., 2000)**.

Additionally, the common association of pediatric obesity with increased growth velocity was also noted. MC4R mutations represent a significant cause of obesity in morbidly obese children and adults (0.5–6%). At least 27 different mutations in 68 individuals have been described **(Clement and Ferre, 2003)**. MC4R agonists are now under development and might be used in the future in patients with decreased melanocortinergic activity

***vi*- Other genes**

●Through genome-wide study, the researchers identified a strong association between an increase in **BMI** and a variation, or "allele", of the **fat mass and obesity associated (FTO) gene**. The **FTO gene** was first discovered whilst studying the DNA of a cohort of patients with type 2 diabetes. The risk of developing type 2 diabetes increases significantly for obese people **(Fraying *et al*., 2007)**.

Through its effect on BMI, **Fraying *et al*., (2007)** found that people carrying one copy of the FTO allele have a 30 per cent increased risk of being obese compared to a person with no copies. However, a person carrying two copies of the allele has a 70 per cent increased risk of being obese, being on average 3kg heavier than a similar person with no copies. Amongst white Europeans, approximately one in six people carry both copies of the allele.

●●Candidate genes also include genes involved in pathways of energy expenditure and lipid and adipose tissue metabolism. Beta-adrenergic receptors (*β2* and *β3*) as well as the UCP1 have been the target of many association studies, including studies in children **(Clement and Ferre, 2003)**. The β_3 adrenergic receptor, located on chromosome 8, is a regulator of energy expenditure and lipolysis. A missense mutation in this gene, characterized by the replacement of tryptophan by arginine at codon 64 (Trp64Arg), is associated with obesity in some studies **(Clement *et al*., 1995; Walston *et al*., 1995)**.

Researchers also identified a UCP2 **gene** in obesity-resisting mice; its gene product may act to raise the body temperature, necessitating an increased use of calories. Conversely, malfunctioning UCP2 may increase the likelihood of fat accumulation, as the requirement for the expenditure of calories is less.

●●●An SNP of gene encodes an ecto-phosphatase, was found to associate with childhood obesity and also with insulin resistance **(Meyre *et al*., 2005)**. Further studies in other populations will be required to establish the

reproducibility of these observations. Very recently, using such an approach, **Herbert *et al*. (2006)** have identified an SNP close to the Insig2 gene which, when present in homozygous form, increases the odds ratio for obesity by 1.2–1.3.

●●●●The gene variant most strongly associated with childhood obesity and adult morbid obesity is located near the **PTER gene**, the function of which is not known. This variant is estimated to account for up to a third of all childhood obesity, and a fifth of all cases of adult obesity. The **second variant** associated with child and adult obesity is found in the **NPC1 gene**. Previous studies in mice have suggested that this gene has a role in controlling appetite, as mice with a non-functioning NPC1 gene suffer late-onset weight loss and have poor food intake. This gene variant accounts for around 10 per cent of all childhood obesity and about 14 per cent of adult morbid obesity cases **(Herbert *et al*. 2006)**.

The final variant is found near the **MAF gene**, which controls the production of the hormones insulin and glucagon, as well as chains of amino acids called glucagon-like peptides. These hormones and peptides are known to play key roles in people's metabolisms by metabolising glucose and carbohydrates in the body. In addition, glucagon and glucagon-like peptides appear to have a strong effect on people's ability to feel 'full' or satiated after eating. This variant accounts for about 6 per cent of early-onset obesity in children, and 16 per cent of adult morbid obesity.

7-Genetics and obesity treatment

Genetics play very important role in obesity treatment in a combination with diet, exercise and behavior modification. Studies of the genetics of human obesity will continue to aid scientific understanding and fuel clinical advances in a number of ways **(Farooqi and O'Rahilly, 2006)**.

Also, genetics will continue to provide new knowledge regarding the normal physiology of energy balance. Knowledge of the specific molecular mechanisms in this and other genetic disorders should lead to better mechanism-directed pharmacotherapy in the future.

It is likely that further discovery of causative genetic defects in humans and experimental animals will continue to highlight other molecular elements of the control pathways for body weight. Thus, genetics will continue to teach us how the normal systems controlling energy balance are wired up and how they function **(Farooqi and O'Rahilly, 2006)**.

Genetics will increasingly aid drug development and better drug targeting to specific patients. Molecules discovered to be involved in energy homeostasis through genetics will immediately become therapeutic targets, the pharmacological manipulation of which may be of use in the treatment of obesity. In this way, genetics will continue to provide therapeutic

targets for the pharmaceutical industry and aid their development of novel compounds for the treatment of obesity.

Genetics may also help to guide drug use in particular patients, so-called 'pharmacogenomics', as individuals with specific types of molecular defect are likely to respond differentially to different drugs. So genetics will also help us to better target drug therapy.

Farooqi and O'Rahilly, (2006) indicated that genetics will improve the targeting of behavioural/ dietary strategies for the prevention and treatment of obesity. It is likely that common genetic variants will selectively influence an individual's response to environmental stimuli and that those of a particular genotype, for example, will be less likely to respond to particular subtypes of dietary intervention than others.

There are already examples of interactions between genes and dietary factors **(Luan et al., 2001)** in the determination of metabolic status, and knowledge of gene– environment interactions will increasingly play a role in the improved targeting of behavioural interventions for the prevention of obesity.

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