Genetics of Human Obesity

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Introduction

For a considerable period of prehistory, hominines were primarily hunter-gatherers. In that period as the food was severely limited, the natural selection favored humans who had the capability of storing energy as fat. As food nowadays is relatively easily available it may be influencing our genome, resulting in a different selective process from past events. On the other hand, the changes in our environment have been occurring more rapidly than the evolution in our genetic makeup. In fact, our genetic background is not very different since around 12,000 years ago, which correspond to the beginning of the agriculture development [1]. This means that there could be a delay in the adjustment of the genetic profile to environment, and that our genetic background would be similar to the one from the time our forefathers were foragers.

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This interpretation result from the "thrifty gene" hypothesis proposed by Neel for a possible evolutionary perspective of obesity [2, 3]. Therefore, when considering the incompatibility between our modern lifestyle and our "ancient" genetic profile, it is understandable why so many people gain weight so easily. When human morphology is considered, there are profound individual differences, such as body size, hair color/form, eyes color/form, etc. These human variations were due, in part, to evolutionary forces, environmental conditions, and cultural differences. However, in all societies and subpopulations, there are both obese and lean individuals. The difference may have arisen, at least in part as a consequence of genetic factors, as is revealed by the high incidence for body mass index (BMI) (40–70 %) [4–7]. These features have been studied by anthropologists who work mainly to assess variation in physical size, shape of the body and the skull in humans using some anthropometric measures that can provide fundamental data and clues regarding the cause of human variation. A trait can reflect the activity of a single-gene (Mendelian or monogenic) or more than one gene (polygenic); both cases, being influenced by environmental factors. The polygenic multi-factorial condition reflects the additive contribution of several genes conferring different degrees of susceptibility. Accordingly, we may understand a polygenic trait as the combined action of several genes producing a "continuously varying" phenotype.

With the advent of the Human Genome Project (1990–2003), millions of DNA sequence variants

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were discovered in the human genome. This large and diverse database of polymorphism markers and the advancement of genotyping technology provided a novel opportunity to study the human genetic basis of several complex diseases through population approaches. In the studies designed for population approaches, a significant amount of individuals must be screened for a large number of polymorphisms. If a variant increases susceptibility to a specific disease of interest, we should note that it is more common among individuals affected by this condition than among non-affected individuals. Thus, through the genotyping of large number of individuals, the population genetics tools are able to highlight the genetic basis of polygenic diseases, such as obesity. This chapter provides the recent knowledge about the genetics of human obesity and covers a part of interactions between our genetic architecture linked to obesity and environmental factors.

The Genetics of Obesity

In the last three decades (from 1980 to 2013), worldwide estimate of the prevalence of overweight and obesity in adults increased ~40 %, with the same trend being observed in children and adolescents [8]. Although the prevalence of obesity is increasing in most countries in the world, partly due to ubiquitous exposure to energy rich foods and to a sedentary lifestyle, not everyone exposed to the current "obesogenic" environment (including also urbanization, education level, and socioeconomic disparities to access a healthy diet) shows unhealthy weight gain [9]. This suggests that there are marked differences in genetic factors that increase vulnerability for BMI. Indeed, evidence suggests that 40–70 % of variance in unhealthy weight gain can be attributed to individual's genetic variations [3, 7].

Moreover, emerging data imply that genetic vulnerability factors interact with environment risk, which is referred to as "epigenetic process". Whereas most scholars consider obesity to be a disorder that results from the interaction between lifestyle and genetic factors, its origin is complex, poorly understood, and most treatments are usually ineffective. Based on genetic and phenotypic characteristics we can consider three types of obesity: monogenic syndromic obesity, monogenic non-syndromic obesity and polygenic (or common) obesity.

Evidence for the Obesity Predisposition Heritability

The pathogenesis of obesity is complex and involves the interactions of several factors among nurture (environmental) and nature (genetic). The simultaneous increase in obesity across worldwide can be principally attributed to changes in the global processed food systems, and to the sedentary lifestyle of modern societies. However, at an evolutionary perspective, genes responsible for high fat accumulation could be advantageous for primitive humans to survive famine periods [3]. But nowadays in an obesogenic environment, this gene function appears to be disadvantageous.

With genetic studies attempting to address the phenotypic variations between individuals, it is not surprising to note that parental obesity is one of the important risk factors for childhood and adolescent obesity [10]. Familial aggregation studies estimate the recurrence risk of obesity within family members, comparing with the general population, it has been shown that individuals who has an obese first-degree relative are about three times more likely to develop an obese phenotype than the subjects in the lean families. For example, Whitaker et al. found that when both parents are obese the risk of childhood obesity increased twice [11]. Other studies, based on parental obesity, found a positive but small to medium effects between children's increased BMI continuing into adulthood [12, 13]. The increased risk of obesity found in families suggests that genes are involved in the development of this condition; however, it could also reflect a general parenting style due to sharing the same environment [14].

The first evidence presented that established the correlation between weight and genetics was in a study performed by Feinleib et al., using 514 veteran twin pairs, and suggesting a genetic influence in obesity risk [4]. In another study based on

this method, Stunkard et al. confirmed this result in a 25-year follow-up study [6]. For this purpose they evaluated more than 4000 monozygotic and dizygotic male twin pairs. They estimated high heritability of BMI at age 20 ($h^2=0.77$) and 45 years old ($h^2=0.84$). In another longitudinal study, Fabsitz et al. studied 514 twin adult veteran males who were of the ages of 48, 57, and 63 years [15]. They found a cumulative effect over time that explains most of the tracking in obesity. These studies were based only in male twin pairs and could represent a sex-specific effect. Nevertheless, other studies using both male and female twin pairs also found a high heritability of obesity, even higher in women (0.73) than men (0.61) [16].

Adoption studies are another way to evaluate the heritability of BMI, comparing adoptees, biological parents, and adoptive parents. Stunkard et al. performed an adoption study to compare BMI of both set of parents with those of the adoptees. They found that, despite sharing the same environment, the BMI of adopted children correlated more strongly with the BMI of their biological parents [5]. Studies based on twins could be more appropriate to assess the contribution of genetics to a given trait (as opposed to environment); in this case, individuals sharing the same genetic and environmental factors. Based on these studies the estimated genetic factors account for 40–70 % of the variations in common obesity.

We must however keep in mind that obesity is a heterogeneous condition, and it is clear that the heritability estimated figures can be influenced by environmental factors. Physical activity could be one of the most powerful influences in the heritability of obesity. Mustelin et al. were able to show that physically active subjects had reduced influence of genetic factors to develop high BMI and waist circumference [17]. Furthermore, other factors such as sex and ethnicity should be incorporated into studies to better understand the gene-environment interactions.

Monogenic Forms of Obesity

Monogenic forms of obesity are described as rare and severe early-onset obesity [18]. Its origin arose from a single gene mutation which is sufficient to cause the increased BMI. Also it represents a small number of cases appearing in childhood, and usually it is accompanied by several neuroendocrine, developmental delay and behavioral disorders. Studies performed in mouse models led to the identification of obesity-related mutations found in monogenic forms of obesity and unveiled important insights into the underlying mechanisms involved in energy homeostasis in humans [19]. Furthermore, studies based on individuals with extreme obesity and on consanguineous pedigrees have been successful in detecting mutations in human genes that cause this form of obesity [18]. Individuals affected by monogenic forms of obesity could be classified into two types based on their phenotypic aetiology.

Non-syndromic forms of obesity is found only in 5 % of the population with an extreme obesity phenotype [20, 21]. Many mutations present for this phenotype are located in a few genes that cause this severe phenotype (Table 7.1). Most of them are involved in the leptin/melanocortin pathway that plays a key role in the hypothalamic regulation of food intake [22].

Syndromic forms of obesity includes about 30 Mendelian inheritance disorders in which individuals, in addition to an extreme obese phenotype possess a distinct set of associated clinical features, such as cognitive deficit or organ-specific developmental abnormalities [23, 24]. Prader-Willi, mental retardation WAGR, Alström, Cohen and Bardet-Biel syndromes are some of the well characterized of the most common form of early-onset syndromic obesity for which the genetic basis is partially understood [3] (Table 7.2).

Genome Approaches for the Study of Common Obesity

There are several approaches to search for genetic variants for common obesity. With the advent of public databases of genetic variants and new genotyping technologies, several strategies appeared with the promise to unveil our knowledge about the genetic of obesity. Recently, the advent of the Next-Generation Sequencing

Table 7.1 Genes related with non-syndromic forms of obesity

Gene symbol	Gene name	Chromosome localization	Obesity phenotypes
LEPR	Leptin receptor	1p31	Extreme early onset obesity, hyperphagia
POMC	Proopiomelanocortin	2p23.3	Early onset obesity
PCSK1	Proprotein convertase subtilisin/kexin type 1	5q15-q21	Childhood onset obesity
SIM1	Single-minded family bHLH transcription factor 1	6q16.3-q21	Early onset obesity, hypotonia
LEP	Leptin	7q31.3	Extreme early onset obesity, hyperphagia
NTRK2	Neurotrophic tyrosine kinase, receptor, type 2	9q22.1	Obesity, hyperphagia, developmental delay
BDNF	Brain-derived neurotrophic factor	11p13	Severe obesity, hyperphagia, body weight
MC4R	Melanocortin 4 receptor	18q22	Early onset obesity, hyperphagia, increased fat mass
MC3R	Melanocortin 3 receptor	20q13.2-q13.3	Increased fat mass

Table 7.2 Most common forms of obesity syndromes

Syndrome	Additional clinical features	*Locus*
Prader-Willi syndrome (PWS)	Cognitive deficit, short stature, hypotonia, hypogonadism, and peculiar facial features	15q11.2-q12
Bardet-Biedl syndrome (BBS)	Cognitive deficit, conerod dystrophy, morphological finger abnormalities, dyslexia, renal disease	11q13, 16q21, 3p13, 15q22, 2q31, 20p12
Alström syndrome	Short stature, retinal dystrophy, diabetes	2p13
Cohen syndrome	Microcephaly, hypotonia, opthalmopathy, several facial features	8q22
WAGR syndrome	Cognitive deficit, Wilms' tumor, aniridia, genital and urinary problems	del11p
Ciliopathies	Retinal degeneration, renal disease, cerebral anomalies, congenital fibrocystic diseases of the liver and pancreas, skeletal dysplasias, diabetes	Several (> than 40 genes)

(NGS) may open new windows in the discovery of new genetic variants that predispose to the obese phenotype.

Linkage Analysis

Family-based genome-wide linkage scans the location of a disease causing *loci* by looking for genetic markers that co-segregate with disease-related phenotypes of interest within pedigrees. A number of different studies, designed on this approach, have successfully localized the cause of a rare Mendelian inheritance pattern [25, 26].

Candidate Gene Studies

The candidate gene approach has been widely used before Genome-Wide Association Studies (GWAS). In this method, researchers used selected candidate genes for specific traits or disorders with known biological function that directly (or indirectly) influence the trait/disorder under investigation. However, the main limitation of this approach concerning *loci* selection is that we need to know the function of the gene to be studied. Furthermore, candidate genes also have a low success rate, with only a few genes (~20) associated positively with common obesity [23].

Genome-Wide Association Studies

The GWAS approach has been possible due to the completion of the Human Genome Project (1990–2003), in which millions of genetic variants were discovered and catalogued into databases, and also with the advancement of chip genotyping technology conducted by the HapMap project (initiated in 2002). This method tests links between genotype/phenotype across hundreds of millions of genetic variants. Especially since 2007, an avalanche of results from GWAS emerged in the literature contributing to a major impact on our current view of the genetic susceptibility risk to common obesity.

New Approaches for the Study of Common Obesity

The advent of new approaches, such as next generation sequencing (NGS) technology provides a new way for molecular diagnosis, identifying rare variants associated with Mendelian or complex traits (such as obesity) within the whole exon or whole genome. This new method is time and cost-efficient in comparison to classical Sanger sequencing approach, and more powerful to detect mutations in novel genes not previously detected by other techniques listed [27]. Hence, since 2013 more and more studies appeared in the literature using this approach to identify genetic variants associated with obesity [28, 29].

Genes Associated with Common Obesity Discovered by GWAS

Recent GWA studies on human obesity field dramatically increased the identification of new genes associated with obesity-related traits. Common obesity is a heterogeneous condition, and unlike monogenic forms, it is expected to result from the interaction of several genes, each contributing with a small effect [30]. The first *locus* associated with obesity was identified in 2007, constituting a cluster of several single-nucleotide polymorphisms (SNPs) located in chromosome 16q12 within the first intron of the fat-mass and obesity associated (*FTO*) gene [31]. Few weeks later, another study confirmed the same intronic cluster in *FTO* gene as being significantly associated with BMI in European populations [32]. For the rs9939609, the most common *FTO* polymorphism studied worldwide, each additional risk allele (minor allele frequency) causes an increase of 1.5 kg in weight, representing approximately a 0.39 higher BMI [33–39]. After these findings the GWAS discovered many other obesity-susceptibility genes.

The *MC4R locus*, is well known for its role in the monogenic forms of obesity and was the second obesity susceptibility gene identified for common obesity [40]. The rs17782313 SNP resides in a noncoding intergenic region at chromosome 18q21, 188 kb downstream of *MC4R* and has the highest significant signal after the *FTO* gene. Another study found the rs12970134 SNP is located in the same region, 145 kb downstream of *MC4R* gene, which increases the risk of obesity among individuals of European descendants [41]. Subsequently, several SNPs in the same gene have been found associated with obesity and ubiquitously present in several European populations, African American, as well as in Asians [42–45].

Willer et al. performed a meta-analysis for BMI in Caucasians and, while confirming the association between the *FTO* and *MC4R* gene, they found six new *loci* associated with obesity including *MTCH2*, *GNPDA2*, *KCTD15*, *SH2B1*, *NEGR1* and *TMEM18* [46]. At the same time, Thorleifsson et al. discovered seven new *loci* near or in genes *BDNF*, *SEC16B*, *ETV5* and *FAIM2*, as well as in *FTO* and *MC4R* associated with obesity in a sample of 31,392 individuals from Iceland population [42].

A recent collaboration between several investigators established the Genetic Investigation of ANthropometric Traits (GIANT) [39]. This consortium expanded its genome-wide association including meta-analysis to include a total of 249,796 individuals of European ancestry. They confirmed 14 previously known obesity susceptibility *loci* and identified 18 new associated with obesity near or inside the genes: *PRKD1*, *SLC39A8*, *GPRC5B*, *MAP2K5*, *QPCTL*, *RBJ*,

LRRN6C, *FLJ35779*, *CADM2*, *TMEM160*, *FANCL*, *LRP1B*, *TNNI3K*, *MTIF3*, *TFAP2B*, *ZNF608*, *NRXN3*, *RPL27A*, *PTBP2* and *NUDT3*. Overall, by 2011, 32 genetic *loci* were found unequivocally associated with obesity by GWAS.

Most recent GIANT meta-analysis comprise 263,407 individuals of European ancestry [47]. Besides confirming the previously 32 *loci* found associated with BMI, they identified seven new *loci*, *ZZZ3*, *RPTOR*, *ADCY9*, *GNAT2*, *MRPS33P4*, *HS6ST3* and *HNF4G*, explaining an additional 0.09 % of the variance in BMI. Until now, 59 genetic *loci* have been robustly found associated with at least one obesity-related trait. More than 35 *loci* have been found associated with the increase of BMI, while other 13 *loci* have been found associated with weight-hip-ratio [48]. Other *loci* such as *LCT* gene have been found associated with BMI and abdominal obesity [49–52], and the *IRS1* and *SPRY2* genes associated with body fat percentage [53].

With the advent of new approach cost-efficient methodologies and the accumulation of more results including meta-analysis it is possible to predict that more genes are present associated with obesity phenotype. All these studies have been performed mainly in adults of European origin. However, in order to develop preventive measures it is important to extend studies in children to understand if candidate genes play any role early in life rather than in adulthood.

Common Childhood Obesity

Further studies on obesity *loci* in children will emerge as an important step for our understanding on variants which are intricately associated with obesity [43]. Moreover, understanding the genetic basis of obesity in children could be a first step to develop preventive measures in early life. In 2011, all 32 *loci* (described above) in GIANT meta-analysis of adult were also tested in a sample of children and adolescents; 1097 obese cases and 2760 lean controls (age between 2 and 18 years) of European Americans were included [54]. They found evidence of association with nine of these *loci*: *FTO*, *TMEM18*, *NRXN3*, *MC4R*, *SEC16B*, *GNPDA2*, *TNNI3K*, *QPCTL*, and *BDNF* with obesity. Overall, 28 of the 32 *loci* showed consistent effects to that found in adult obesity by meta-analysis. In a GWAS for childhood obesity in European descendants, researchers identified two new *loci,* one near the *OLFM4* and another in the *HOXB5* genes [55]. A recent study conducted by the Early Growth Genetics (EGG) consortium replicated findings on all 32 previously found *loci* and the newly *HOXB5* and *OLFM4* genes identified in childhood obesity in a Greek adolescents cohort [56]. They calculated a genetic risk score, based on all 34 *loci* and found that 27 of them showed consistent effects with those reported in adult obese subjects.

GWAS in Other Ethnic Groups

It is also important to confirm information results across different ethnic groups and not restrict studies in European populations only. It is because obesity is no longer a problem of only developed countries but also affects people living in developing countries due to changes in their life style by adopting Western life (changes in dietary habits and a more sedentary lifestyle). Furthermore, human genetic set up can vary between populations (linkage disequilibrium) and even between individuals in regards to obesity susceptibility. Several GWAS performed in East Asian populations identified *FTO* SNPs associated with BMI and obesity [57, 58]. Additionally, the association of *FTO* SNPs with obesity-related traits was also found in Japanese, Chinese, Vietnamese, and Asian Indian populations [36, 37, 59–64]. More controversial results were found for the subjects of African origin [65–67]. Monda et al. observed an association between the *FTO locus* and BMI in individuals belonging to an African ancestry. In a recent systematic review conducted within several African population groups, the researchers also observed several SNPs located in genes such as *ACE*, *ADIPOQ*, *ADRB2*, *AGRP*, *AR*, *CAPN10*, *CD36*, *C7orf31*, *DRD4*, *FTO*, *MC3R*, *MC4R*, *SGIP1* and *LEP* associated with at least one obesity-related trait [68, 69]. Reason for disparity may be due to the lack of quality studies mainly with African groups.

Regarding the extent of the effects of each additional copy of the risk allele on the *FTO locus*, differences can be observed between Asian

and African populations relative to subjects of European descent. The effect of risk allele increases BMI by 0.16 in East Asian, 0.20 in Indian Asian and 0.10 in African descendants, which is less than 0.39 observed in European descents [70]. When comparing the minor allele frequencies for *FTO* SNPs, in East/Indian Asians they range between 12 and 33 %, in African populations 7–18 %, which is still lower compared to the 42 % found in European populations [70].

In near future it would be important to increase GWAS meta-analysis to establish how strongly obesity-susceptibility *loci* are associated with these ancestries.

The "Missing Heritability" of the Genetics of Human Obesity

Since 2005, due to increased use of GWAS the enthusiasm of the scientific community for the investigation of complex disorders also increased exponentially. As described in the previous sections, GWASs have been successful in identifying several *loci* associated with the susceptibility risk of obesity. However, all together it only explains 1–3 % of the variance in BMI. Hence, there is a gap between the explained variance of BMI due to known SNPs (1–3 %) and the estimated heritability of the BMI variance (40–70 %).

The *FTO* gene still remains endowing highest effect on BMI with only 0.34 % of the total variation. An important concern about the interpretation of the results regarding GWAS is that this approach is based on the "disease-common" variant hypothesis, and variants panels were designed to cover the common genetic variants (minor allele frequency ~45 % in populations) [71]. In this form, current GWAS is not being able to identify rare variants. Recently, this and other different kinds of genetic variations were pointed as the possible source of the missing heritability genes and this is required to be explained in obesity, because the effect size could be higher in rare and low frequency alleles (<5 %) than in common variants (~45 %).

A recent novel approach called Genome-wide Complex Trait Analysis (GCTA) has been proposed to estimate variance, explained by all variants in a *loci* or in the whole genome for a complex trait rather than testing the link between a particular variant to the trait [72]. The main aim of this method is to unveil the "missing heritability" caused by the inability to detect a large number of common variants with small effects or rare variants with large effects by GWAS. In case of obesity, all together it accounts for up to 17 % of the overall BMI variance in adults [73]. In a recent analysis of twin children, Llewellyn et al., found that the additive effects of multiple common variants are 37 % of the BMI variance. In another study, the same authors, based on the same approach, suggested an increased genetic influence on adiposity during childhood [74, 75]. Therefore, it is expected that part of the missing heritability could be due to rare genetic variants, copy number variations (CNVs), and epigenetic factors. Despite all this arguments, it is clear that there still remain many variants to uncover relationship between genetics and obesity.

Rare Single Nucleotide Polymorphisms

The current arrays of genotyping technologies are designed to cover common genetic variants and not only to detect variants below 5 % frequency based on the 1000 Genome project. So, most of GWASs have been focusing in search of common genetic variants associated with BMI (>40 %), without including the rare variants. Nevertheless, the effect size of rare alleles is higher than common variants in causing disease, and in some cases with high penetrance. Blakemore et al. found a low frequency variant located in the *NAMPT* gene associated with severe obesity in Caucasian children [76]. The rs10487818 variant presents a minor allele frequency in general Caucasian population of <1 % in and was not found in African and Asian groups. However, the researchers observed a strong protective link between the minor allele, which was markedly stronger in the severely obese children compared to the class III obese adults. It is possible that the rare variants could be ethnic-group specific. Today, several studies emerged analyzing the potential effect of rare obesity-susceptibility genetic variants with

Table 7.3 Some candidate CNV *loci* found to be associated with obesity

Locus	Localization[a]	Genes overlap	Reference
2p11.2	chr2:88,422,508-88,427,650	*FABP1*	[82]
2p11.2	chr2:89,285,770-89,461,034	*None*	[82]
4q25	chr4:108,285,188-108,293,270	*None*	[84]
5p15.33	chr5:795,720-851,101	*ZDHHC11*	[82]
8q24.3	chr8:143,545,377-143,612,149	*BAI1*	[82]
10q11.22	chr10:46,338,178-46,812,351	*GLUDP2, PPYR1, GPRIN2, SYT15 BMS1P2, LOC642826, LOC643650, ANXA8L1, CTGLF7, LOC728643, LOC728657, LOC100132646, FAM25B, LOC100133189*	[82, 84, 86]
10q11.22	chr10:47,011,183-47,145,122	*LOC340844, LOC728684*	[84, 86]
10q26.3	chr10:135,178,653-135,227,268	*CYP2E1*	[87]
10q26.3	chr10:135,092,863-135,146,259	*CYP2E1*	[87]
11q11	chr11:55,130,596-55,210,165	*NEGR1*	[86]
11q11	chr11:55,130,596-55,210,165	*OR4P1P, OR4V1P, OR4P4, OR4S2, OR4C6*	[84]
11q13.4	chr11:72,307,637-72,353,420	*PDE2A*	[83]
15q11.2	chr15:24,803,304-24,808,624	*PWRN1*	[88, 90]
16p11.2	chr16:30,907,928-30,914,880	*CTF1*	[83, 89]

[a]Chromosome position is based on genome build hg18

obesity that can explain part of the missing heritability [77–80]. However, it will be possible that undiscovered common variants themselves might explain the missing fraction of genetic of human obesity.

Copy Number Variations

Copy number variations (CNVs) result from deletions and duplications of chromosomal segments constituting a major source of the individual humans' variation as single-nucleotide polymorphisms. Some of them encompass large parts of genes, with the replicated or deleted copies having a potential functional effect. This common type of genomic variability has been suggested as a possible cause for the missing heritability. Currently, several large (>500 kb) and rare (<1 kb) CNVs have been reported linked to obesity including 16p12.3, 16p11.2, 11q11, 10q11.22, etc. [80, 90] (Table 7.3). Some of these CNVs are in strong linkage disequilibrium with adjacent SNPs [82, 85]. The most established CNV associated with obesity correspond to a chromosomal deletion of at least 593 kb at 16p11.2. Heterozygotes for this CNV have been significantly associated with obesity in Caucasian individuals with severe early-onset obesity and cognitive deficits [89]. This deletion was absent from healthy non-obese controls and accounted for 0.7 % of morbid obesity cases (BMI ≥40 kg/m^2), with an odds ratio of 43.0, demonstrating the strong effect of rare variants [89]. Bochukova et al. identified several CNVs that contribute to obesity in a Caucasian sample, including the 16p11.2 [83]. An interesting result observed was the fact that all 16p11.2 deletions found in a sample of 1062 patients with severe obesity encompass several genes including the *SH2B1*, which is known to play a role in the leptin and insulin signaling [83]. Sha et al. found one CNV at 10q11.22 that contribute to 1.6 % of BMI variation and covering the important *PPYR1* obesity-related gene, that was a key regulator of energy homeostasis and food intake [82].

In a sample of children and adolescents from the German population, 20 CNVs were found to be directly linked with obesity, with one region (11q11) that covers three olfactory receptor genes *OR4P4*, *OR4S2* and *OR4C6* [86]. These genes interact with odorant molecules in the nose,

giving a perception of smell by neuronal response of the olfactive stimuli. Furthermore, Sun et al. found that the CNV *locus* 8q24.3 playing significant roles in obese Chinese children [81]. However, they failed to achieve any significant association with the well-reported 10q11.22 and 16p.11.2 *loci* in their sample. This result could be due to environmental and cultural difference between Asian and Caucasian populations, and these CNVs obesity-associated genes could have different expression. CNVs are still poorly studied in the context of obesity. However, studies in this field at least were able to demonstrate that they could play an important role in the missing heritability that still needs to be explored.

Epigenetic Factors

Epigenetic is defined as the study of heritable changes, which affect gene function but do not involve changes in the DNA sequence [91]. These factors include genomic DNA methylation, changes in chromatin organization by histone modifications, and non-coding microRNAs (microRNA) [92]. In a simple analogy, it is like genetics refers to the genes "writing", while epigenetics to the genes "reading". So, in the same genetic sequences, gene expression may vary due to inter-individuals differences, which could be programmed by environmental factors.

Epigenetic markers can change during lifetime and have a heterogeneous distribution in tissues. DNA methylation is a well-known epigenetic marker. It has a methyl group at the carbon-5 position of cytosine, at the CpG dinucleotides position, and is usually associated with gene silencing in the promoter regions [91, 93]. The *Agouti* mouse viable yellow (A^{vy}) model is one of the best-studied examples on how early environmental exposures interact with epigenetic gene regulation influencing the phenotype [94, 95]. The murine *agouti* gene influences DNA methylation at early developmental phase, affecting coat colour, which correlates with adult body weight. When the *agouti* gene is kept in the "*off*" position (by attaching methyl groups to prevent transcription), mice have a brown fur and slim healthy, whereas when the same gene is turned "*on*" (unmethylated) the mice present a yellow fur and an obese phenotype. Interestingly, there is a wide variation in individual coat colour and obese phenotype varying due to the mother's diet as well [96, 97]. This phenomenon occurs by epigenetic modifications of *agouti* gene in early developmental phase. Basically, the phenotype variations are caused by DNA methylation patterns that are acquired during early embryonic development and passed over through the female germline that results in stable intergenerational transmission [98–100].

Several other studies have been performed based on the link between obesity and DNA methylation. Using a genome wide approach, obesity has been related to changes in DNA methylation status in peripheral blood leukocytes of lean and obese adolescents in the *UBASH3A* and *TRIM3* genes [101]. Godfrey et al. found that 31 CpGs with higher methylation levels at birth strongly correlated with greater adiposity in later childhood [102]. Analyzing the methylation profile on a genome-wide scale by sampling DNA from peripheral whole blood, Almén et al. observed that individuals with the rs9939609 polymorphism risk allele affects the methylation status of sites related to genes *KARS*, *TERF2IP*, *DEXI*, *MSI1*, *STON1* and *BCAS3*; showing that *FTO* gene may influence the methylation level of other genes [103]. In a recent study, Zhao et al. observed that the hyper-methylation of the promotor of the *SLC6A4* gene was associated with an increase in BMI, body weight and waist circumference [104]. Xu et al. by analyzing 470,000 CpG sites in adolescents found a differential variability in CpG sites, which was more variable in obese than in lean individuals, constituting an important feature in obesity related to methylation [105]. Nevertheless, most of DNA methylation sites found until now associated with obesity is required to be confirmed. Studies based on this marker undoubtedly will permit to establish an epigenetic basis for human obesity.

Studies based on pre-conceptual, *in utero*, and postnatal developmental environment showed also to have an important impact in long-term risk for adult-onset obesity by a set point of adaptive changes. Environmental conditions experienced *in utero* may have a life-long effect in the propensity to develop obesity that constitutes a

"critical period". As previously reported in the heritability section, there is an important association between maternal obesity and childhood obesity. Relton et al. presented evidence that some DNA methylation patterns varies at birth and showed its association with BMI, fat mass and lean mass at the age of 9 years [106]. This observation suggests that variation in DNA methylation patterns at birth in multiple target genes may influence body size in childhood. Moreover, maternal diet can alter later the child's adiposity, accompanied by epigenetic changes in genes controlling the energy homeostasis. Parental preconceptional environmental exposures could also have an effect on the health status of the offspring in later life. In two recent studies regarding parental obesity an association has been observed between DNA methylation profiles at *MEST*, *PEG3*, and *NNAT* genes in children born from obese parents, when compared with children born from non-obese parents [107, 108]. These results points to a pre-conceptional influence of parental life-style or over-nutrition in the reprogramming of imprint marks during gametogenesis and early development [107, 108]. Hence, experienced perinatal events are important in defining the epigenetic marks that will persist until the adult age. However, our knowledge about mechanisms underlying maternal nutritional environment that induces changes in their offspring remains largely unknown.

Continuous advances in research show promising results about the implication of epigenetics mechanisms in the etiology of obesity. Epigenetics has shown that our genes *per se* are not the only factor to determine our phenotype and that our behaviors can alter the expression of our genotypes. Rönn et al. observed a change in the level of several DNA methylation sites, which were altered in response to a 6-month exercise intervention [109]. This result showed that our behavior can modulate the susceptibility to develop obesity. Despite the high number of DNA methylation candidate genes and some epigenome-wide association studies (EWAS), most of the associations have not yet been confirmed by other samples whether those CpGs are reliably associated with obesity.

Interaction Between Genetics and Lifestyle Factors

The population based genetic profile is only a small portion of the susceptibility risk to develop the obese phenotype. In addition to genetic variants, other mechanisms could lead to differences in obesity risk in individual subjects. Interactions between environment factors and genes are another potential explanation for the unexplained heritability. The exposure to an environmental factor should increase the magnitude of relative risk if a genetic susceptibility is present (gene-environment interactions, see epigenetic section). Furthermore, several studies found evidences of the cumulative effect of common genetic variants that predispose to obesity with lifestyle factors.

Gene-Gene Interaction (Epistasis)

The study of the heritability of complex traits can be difficult as it may involve a single gene or interactions between several genes. Approximately 20,000 genes are present in human genome with a set of complex interactions among genetic *loci* to produce phenotypic characteristics. Some of the best examples of interaction between two or more genes to produce traits are: *Rose-comb* and *Pea-comb* alleles in chicken, flower color in sweet peas, or flower petal color of *Primula* plant [110, 111]. These simple examples covering Mendelian inheritance have been more successful in identifying the genetic cause of the phenotypic variability than complex traits such as diabetes, obesity and hypertension, which could result from the contribution of a considerable number of *loci* [112].

In the past most GWASs on obesity were focused on the association of a single-*locus*, in which each variant was tested individually with specific traits without studies on gene-gene interactions. Speliotes et al. performed a GWAS discovering 18 new *loci*, and confirming 14 known obesity-susceptibility *loci* with BMI [39]. These authors tested a SNPxSNP interaction but found no evidence of association after multiple test correction. One reason for this lack of success in genetic studies of complex disorders may be due to the specific failure to take into account the existence of interactions between *loci* [113].

Although major interest can be seen on studying the relationship between gene-gene interactions in complex disorders, few studies can be found on the influence of epistasis on obesity risk. In a sample of women with bulimia nervosa, Kaplan et al. analyzed the possible role of *BDNF*/*DRD4* gene-gene interactions [114]. They found that individuals with both Met66 allele of *BDNF* and 7R allele of *DRD4* had higher BMI than individuals without those variants. Also two studies conducted in the Chinese population investigated and found an interaction and contribution to obesity risk including abdominal obesity of several variants located in the peroxisome proliferator-activated receptors (PPARs) in their contribution [115, 116]. Using a genome-wide association scan for the effect of epistasis on BMI in four European populations, Wei et al. found eight epistatic pairs that could explain a proportion of the BMI variation, and Young et al. found one Gene-Gene interactions (*PRKD1-FTO*) after multiple correction test in a sample of European descendant adolescents on BMI [117, 118].

Evidence is available that epistasis can help to understand the quantitative effects of gene interactions of complex genetic networks. Furthermore, interactions between genes result from a long evolutionary process. However, the study of epistasis related to complex traits is not easy due to the putative high number of possible genes interactions.

Link Between Nutrition and Genomics

Nutrition appears to be one of the most important factors contributing to the obesity susceptibility risk. It is clear that an increase in food intake along with sedentary life style brings high risk for the obesity. Furthermore, there is some evidence that food consumption can modify patterns of gene expression influencing the phenotype [119]. The recent research continues trying to understand the variability in metabolic response to diet and food quality (nutrigenomics).

Human diet has been suffering from a profound alterations marked by innovations in food technology (processed food). Moreover, nutrients that are being complicated by several bioactive compounds with molecules carrying components from the external environment may affect the process of gene expression when we consume them [120, 121]. It is well known that several dietary components can modulate epigenetic phenomena by inhibiting enzymes such as DNA methyltransferases and histone deacetylases [119]. Furthermore, several studies found an interaction between genetic variants on nutrient requirements (nutrigenomics). For example, Ortega-Azorín et al. found a gene-diet interaction of the *FTO* rs9939609 and *MC4R* rs17782313 polymorphisms with adherence to the Mediterranean diet on type 2 diabetes, in which this type of diet counteracts the genetic predisposition [122]. Steemburgo et al. observed that individuals carrying both minor alleles of the rs9939609 polymorphism were positively associated with a higher intake of total fat and low-fiber consumption, independent of BMI [123]. Obesity susceptibility genes, *FAIM2*, *FLJ35779*, *FTO*, *LRRN6C*, *RBJ*, and *SEC16B*, were found to interact with dietary carbohydrates to increase BMI [124]. Other *loci* such as *ADRB2* and *MC4R* were also pointed for relationship with carbohydrates intake [125].

The periconceptual *in utero* and postnatal developmental environment can also play a role on long-term risk for adult-onset obesity by a set of adaptive changes. Breastfeeding has recently been pointed to protect against childhood obesity and the authors observed an association between DNA methylation of *LEP* gene with early life environment [126].

Despite the increased number of studies showing that nutrients indeed influence epigenetic modifications (e.g. genistein, curcumin, tea polyphenols, etc.) the interaction of nutrients with biological systems remains mostly speculative.

Link Between Physical Activity and Genomics

Physical activity is another important component involved in the complex etiology that influences obesity. The practice of a regular exercise could be an important factor for preventing and reducing weight gain, as well as other health and psychological benefits. Several studies found an interaction of *FTO locus* with physical activity is important in the obesity-susceptibility putting emphasis that a moderate or active physical

activity attenuates the association of *FTO* variants with increase BMI [127–131]. A meta-analysis conducted by Kilpeläinen et al. observed that the minor risk allele of the *FTO* rs9939609 polymorphism increased the odds ratio of obesity by 1.23-fold/allele, but this increased is attenuated by 27 % in physical active individuals (p interaction = 0.001) [132]. Similar result was found in another meta-analysis conducted by Ahmad et al. that combining 12 polymorphisms showed a significant genetic-risk-score and physical activity interaction effect in obesity (p interaction = 0.015) [133]. These results support the notion that individuals with moderate or higher levels of activity may attenuate the influence of obesity susceptibility polymorphisms on BMI.

Interestingly, some studies provide evidence that the propensity to be active can have involvement of genetic components in both animals and humans [134]. Studies based on family aggregation observed that in a family with more active parents, children have tendency to be more active than children in inactive parents [135]. Some variants have been found associated with inactivity such as variants located in the *MC4R* gene have been found to be related to inactivity, using a self-reported physical inactivity questionnaire in French-Canadian families and Mexican-Americans [136, 137]. The Gln223Arg variant located in the *LEPR* gene was also found associated with lower 24 h energy expenditure and physical activity levels in individual homozygotes for the Arg223 allele when compared to Gln223 allele in Pima Indians populations [138].

These are only few examples about a possible interaction between some genetic variants and variation in physical activity. More studies are needed to identify *loci,* which could be implicated in this interaction to reveal and help to understand the causes that contribute to the development of the obese phenotype. However, these results indicate that it is important to practice a regular activity level to maintain a healthy weight.

Drug-Genotype Interaction

Drug therapy option for obesity could be suggested for subject with a BMI >30 with existing co-morbidities such as diabetes, dyslipidemia or hypertension [139]. In the last one decade, the concept of "pharmacogenetics" emerged as a field investigating if the consumption of certain drugs was affected by the genetic variation of individuals [140]. This new field of investigation focuses the attention towards the study of genetic variants within one or more candidate genes for links with pharmacologic phenotypes. It was found that ingestion of certain bioactive compounds interacted with some functional variants and could alter the response to pharmacotherapy affecting drug metabolism, drug transport or drug targets [139, 140].

Currently available drugs in the market for controlling obesity, approved for continuous use in the United States of America (USA) are: orlistat (Xenical®, Alli®), lorcaserin HCL (Belviq®), phentermine and topiramate extended release (Qsymia™) [139]. Orlistat alters metabolism by inhibiting the gastro-intestinal absorption of triglycerides and Lorcaserin HCL and Phentermine act centrally as an appetite suppressant [139, 141, 142]. Recently, the US Food and Drug Administration (FDA) approved the glucagon-like peptide-1 (GLP-1) agonist Liraglutide (trade name Saxenda®, Novo Nordisk), initially used for the treatment of type 2 diabetes, which on clinical trials was found to have significant effect on reductions in body weight due to its appetite-suppressing effects [143].

It is possible that in future such pharmacologic intervention can become a powerful tool for obesity control. Based in the personalized genetic profile it could be possible to determine which sub-populations will respond optimally to which particular drug. This field may open an important area of research with the necessity to identify differences in drug response and tolerability, and investigate gene regulation, epigenetic modifications, and DNA-protein interactions that could explain individual differences in responses to drugs beyond genetic variation.

Bariatric Surgery

Generally, in patients with a BMI greater than 35 and suffering from severe obesity-related co-morbidities, after failing diet control, exercise, and

drug therapy, a surgical intervention could be an option for losing weight. However, some patients present a significant weight gain after surgical intervention. There are several guidelines and procedures that surgeons/gastroenterologists need to follow before a possible surgical treatment of obesity due to the associated risk [144]. We will not detail about surgical intervention strategies, which have been reviewed elsewhere as well in this book in chapter 23 and in reference [145]. However, below we present about a possible relation between certain genetic variants and the success rate to maintain weight loss after surgery.

It is now well established that genetics factors play in the etiology of obesity. There is a high degree of inter-subject variability for surgical outcomes, so genetic profile should be taken into account in patients undergoing bariatric surgery [146]. Generally, patients submitted to surgical intervention have a durable weight loss [147]. However, despite its effectiveness after the intervention not all patients maintain the healthy weight or obtain the same clinical benefits. Several studies emerged linking specific variants in response to bariatric surgery. Moore et al. found that patients carrying a rare *MC4R* allele associated with obesity, lost less weight after surgery than non-carrier patients [148]. After performing a follow-up study, de Luis et al. observed that individuals homozygous for the rs6923761 G allele (*GLP-1R* gene) showed higher weight loss after a biliopancreatic diversion than individuals carrying the A allele [149]. Furthermore, Hatoum et al. found a significant association of the 15q26.1 *locus* with weight loss after Roux-en-Y gastric bypass surgery [147]. In another study using the same intervention, 17 variants were found associated with weight loss 2 years after the surgery [150]. Hence evidences exists regarding the use of genetic variants to identify response to surgical procedures [147, 151, 152]. In a complex disorder such as obesity, the identification of genetic contributors could be useful to select those individuals who will obtain required weight-reducing effects to benefit and not subject them to go to an invasive technique. However, these results need to be interpreted with caution, as there are inadequate data available.

Gut Microbiota and Obesity

The human intestine is colonized by a variety of microorganisms, which are collectively known as microbiota. This complex community contains more than 100 trillion bacteria in the gastrointestinal tract that co-evolved and co-adapted in response to environmental selective pressures over hundreds of millions of years [153]. The gut microbiota live in a perfectly mutualism relationship with its host, which is beneficial to both organisms as well human. Although certain conserved microbial species are common among the hosts, however individual person seems to have distinct and variable species of gut microbiota probably due to our difference in lifestyle. Several studies showed that the human gastrointestinal tract is colonized by microbiota during and shortly after birth, and subsequently influenced by various factors, such as age, sex, stress, surgery, medication, nutrition, and the genetics of the individual [154] (Fig. 7.1).

Numerous metabolic functions of microbes in gut enable the digestion of food components, such as humans cannot digest certain fibers but bacteria present in the gut have the enzymes glycoside hydrolases and polysaccharide lysate which can breakdown polysaccharides of plant cell wall [155, 156]. Recently, an altered gut microbiota has been suggested to be critical for the development of obesity [157]. Also several human studies have demonstrated a link between the gut bacteria and obesity [158, 159], which it is not surprising when we know that this microbial community can contribute to the host with their genetic makeup. Furthermore, diet is one of the principal factors linked to obesity, having an important impact in the composition and activity of intestinal bacteria. Several studies have found that childhood obesity is higher when both parents are obese, and some of them are attribute to a higher predisposition when the mother has an obese phenotype [11–13]. Also it has been shown that gut microbiota can be inherited from mothers to their offspring [160]. In addition Turnbaugh et al. observed that obese individuals have an altered gut microbiota when compared to lean individuals [161]. This factor could be important to take into consideration for global increase of obesity occurring in the last three decades.

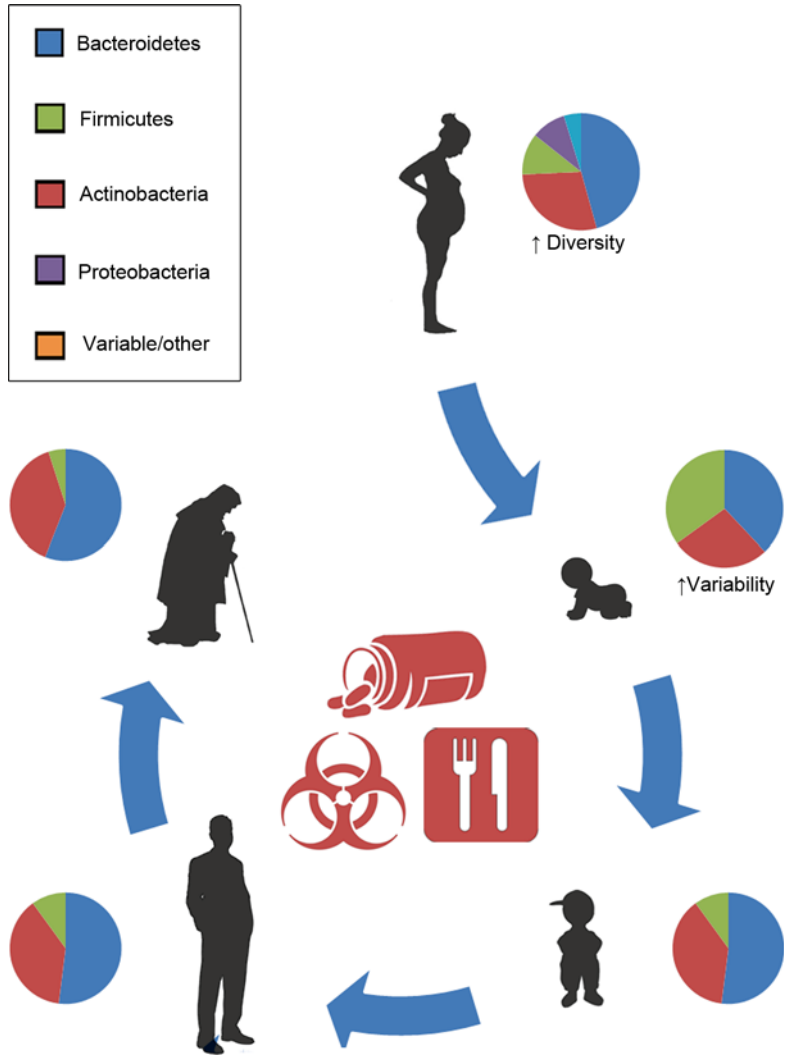

Fig. 7.1 The characteristics at phylum level of the human intestinal microbiota throughout the life cycle. The composition of gut microbiota changes in response to several environmental factors (e.g. diet, antibiotics, bacteria, etc.) and life stages. Prenatal exposure (pregnancy stage) affects and modulates the newborn gut microbiota and is characterized by higher diversity. There is a complex interaction between mother and child, and maternal behavior can negatively influence the newborn gut microbiota composition (e.g. fatty diet, weight gain, stress, smoking, drugs, etc.). On the other hand, infant stage is characterizing by a greater variability and converges into its final adult composition, remaining mostly stable throughout human life. In elderly individuals (>65 year) significant changes in the composition of the gut microbiota have been observed. Some factors such as stress, immune responses, inflammation, and increased susceptibility to infections which can increase the consumption of antibiotics are pointed out

Ley et al. found in a leptin-deficient *ob/ob* mouse model differences in the ratio of *Bacteroidetes* and *Firmicutes* (two of the most dominant species), comparing obese *versus* lean mice [160]. Obese mice presented an increase in *Firmicutes* and a decrease in *Bacteroidetes*. Similar results were found in human gut microbiota between obese and lean individuals [162]. So, if gut microbiota is different between obese and lean individuals, and was inherited from mother to their children, the BMI of mother before pregnancy could be an indicator of part of the missing heritability in childhood obesity.

In a recent study, Parks et al. investigated the interactions between obesity traits, gene expression and gut microbiota in response to a high-fat/high-sucrose diet in mice [163]. They observed a relationship between genotype and gut microbiota plasticity during high-fat/high-sucrose feeding. After a surgical intervention, Damms-Machado et al. investigated gut microbiota composition and dietary weight loss; they found a moderate alteration of the intestinal microbiota after a laparoscopic sleeve gastrectomy [164]. This modification could be explained by weight loss and dietary food restriction mostly due by reduced fiber consumption. Furthermore, treatments based on antibiotics have a real effect on the gut microbiota [165]. However, our knowledge about how the genetic basis affects gut microbiota and interacts with obesity remains limited.

Conclusion

Common obesity results from the interaction of several internal and external factors. Since 2007, with the discovery of the first *locus* associated with common obesity, more than 55 *loci* were found associated with an obesity-related trait and many more are still to be discovered. Rapid developments in genotyping technology in recent years have led to an increase in our understanding of the genetic influences on obesity. At the same time, the progresses on sequencing technology in recent years have become promising to discover new possible variants associated with obesity susceptibility risk. Probably the combination of common with rare, low allele frequency and CNVs may contribute to significant increase in the knowledge of obesity risk. Furthermore, in common obesity both genetic and environmental factors may contribute to susceptibility of developing the obese phenotype, but it is unclear how these factors interact in their influence to the risk. The interaction between genetic or environmental mechanisms may differ among cultures, which result from differences in behavior, diet, environment, and social structures that can influence obesity. Further studies based on genetic epidemiology are needed and probably will be a hot topic in obesity research in the coming years.

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