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Gene-Diet Interactions on Childhood Obesity

Ciências da Nutrição

Faculdade de Ciências da Saúde

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(Diogo Filipe Oliveira dos Santos)

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Orientadora:

Professora Doutora Andreia Oliveira

To my parents, for allowing me to follow my dreams, for the hours I was not present and for being an inspiration.

To all my colleagues and friends of associativism, for being by my side at all hours in these four years for the benefit of all students.

To my friends, for believing and support me.

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I. Abbreviations list

ACE – Angiotensin-Converting Enzyme

APOA2 – Apolipoprotein A-2

BMI – Body Mass Index

CKD – Chronic Kidney Disease

CVD – Cardiovascular Disease

CYP11 β 2 – Cytochrome P450 family 11-subfamily β -2, -aldosterone synthase

ENaC – Epithelial Amiloride-sensitive Na Channel

ENPP1 – Ectoenzyme Nucleotide Pyrophosphate Phosphodiesterase 1

FTO – Fat Mass and Obesity-Associated

GST – Glutathione S-Transferase

GWAS – Genome-Wide Association Studies

GWLS – Genome-Wide Linkage Studies

KCTD15 – Potassium Channel Tetramerization Domain Containing 15

LEP – Leptin

MC4R – Melanocortin 4 Receptor

NEDD4L – Neural Cell Expressed Developmentally Downregulated 4 like

NEGR1 – Neuronal Growth Regulator 1

NPC1 – Niemann-Pick C1

PCSK1 – Prohormone Convertase 1

PPARG – Peroxisome Proliferator-Activated Receptor Gamma

POMC – Pro-Opiomelanocortin

SD – Standard Deviation

SH2B1 – SH2 B adaptor protein 1

WHO – World Health Organization

Gene-Diet Interactions on Childhood Obesity

Interações Genes-Alimentação na Obesidade Infantil

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II. Abstract

Obesity is a global epidemic and in children the number of individuals with obesity increased 2,28 times in the last three decades. Obesity comes with a massive amount of complications such as type 2 diabetes, dyslipidemia and insulin resistance. Obesity is a multifactorial disease and there many risk factors interacting in its development, genetic, behavioral and environmental factors. This paper aims to understand the genetic factors behind this disease and the interactions between the genes and diet that prompts childhood obesity. For the purpose of this paper the literature was searched in English language in the PubMed Central® search engine, totaling 110 papers.

During the last decade, research has tried to understand the gene(s) responsible for the predisposition for childhood obesity, so many studies were conducted such as genome-wide association studies (GWAS). Childhood obesity appear to result from the presence of many risk gene variants, and their response to obesogenic environments. There is evidence that genes like FTO, MC4R, POMC, LEP and LEP receptor have an influence in weight gain and in the development of related complications since early ages. Diet is one of the most important environmental factors believed to contribute to obesity development. Currently, there are two approaches trying to understand interactions between genes and diet, nutrigenetics and nutrigenomics. Both are based in the premise that nutrients/diet components can influence the gene expression process and affect different metabolic pathways that finally will origin the individual's phenotype. Most of the studies accomplished are related to fatty acids metabolism, so to further understand other metabolic pathways more studies are needed. FTO, APOA2 and NPC1 genes are some of the genes that already have some evidence supporting their interaction with dietary fat intake in weight gain, including in children for whom less evidence exists. Genome-wide association studies have increased the knowledge in this area, but they have some limitations, which means that more studies and with different approaches are needed to further understand the relation between genes and environmental factors in obesity. A more personalized diet (under prior knowledge of obesity-related polymorphisms) is currently under discussion in the scientific arena.

Keywords: childhood obesity; diet; gene; gene-diet interactions; children.

III. Resumo

A obesidade é uma epidemia global; o número de crianças com obesidade aumentou cerca de 2.28 vezes nas últimas três décadas. A obesidade tem associadas inúmeras complicações como diabetes tipo 2, dislipidemia e resistência à insulina. A obesidade é uma doença multifatorial que possui vários fatores de risco que interagem no seu desenvolvimento, como genéticos, comportamentais e ambientais. Este artigo ambiciona perceber os fatores genéticos inerentes a esta doença bem como as interações entre os genes e a alimentação que potencializam a obesidade infantil. Para a realização deste artigo procedeu-se a uma revisão bibliográfica da literatura em língua inglesa no motor de busca PubMed Central®, totalizando 110 artigos.

Durante a última década, a investigação tem tentado perceber quais os genes responsáveis por uma maior predisposição à obesidade infantil. Nesse sentido vários estudos foram conduzidos, como por exemplo os *genome-wide association studies* (GWAS). A obesidade infantil parece resultar da presença de genes de risco, bem como da sua resposta face a ambientes obesogênicos. Existe já evidência da influência de genes como o FTO, MC4R, POMC, LEP e recetor de LEP no aumento de peso e no desenvolvimento de complicações associadas desde idades precoces. A alimentação é um dos fatores ambientais mais importantes para o desenvolvimento da obesidade. Atualmente, existem duas abordagens para perceber as interações entre os genes e a alimentação, a nutrigenética e a nutrigenómica. Ambas se baseiam na premissa de que os nutrientes/componentes da alimentação podem influenciar a expressão génica e afetar diferentes vias metabólicas, que finalmente irão originar o fenótipo do indivíduo. A maioria dos estudos conduzidos até hoje estão relacionados com o metabolismo dos ácidos gordos, pelo que para melhor compreender outras vias metabólicas são necessários mais estudos. A interação com a ingestão de gordura no aumento de peso já está evidenciada para genes como o FTO, APOA2 e NPC1, incluindo estudos realizados em crianças para as quais a evidência é mais escassa. Os *genome-wide association studies* permitiram o aumento de conhecimento nesta área, mas apresentam algumas limitações, o que significa que são necessários mais estudos e com diferentes abordagens para melhor entender a relação entre os genes e os fatores ambientais no desenvolvimento da obesidade. Uma dieta mais personalizada (com prévio conhecimento de polimorfismos relacionados com a obesidade) está atualmente sob discussão nos fóruns científicos.

Palavras-chave: obesidade infantil; dieta; genes; interações genes-alimentação; crianças.

1. Introduction

Obesity is nowadays a major public health challenge; it is described as a global epidemic, some authors even describe it as a global pandemic (1–4). Recent estimates point out an epidemiological transition from underweight to overweight and obesity throughout the world (3). The prevalence of overweight and obesity has increased substantially over the past three decades (3). In children, the prevalence of overweight and obesity has risen 47,1% and the number of individuals has increased from 921 million to 2.1 billion in 33 years (2). Nonetheless, the prevalence of childhood obesity in the United States and in some European countries, such as Portugal has apparently reached a plateau (5), but it continues in high rates.

This epidemic comes often followed by high rates of other related diseases or metabolic complications (6,7). Childhood overweight and obesity is now associated with type 2 diabetes mellitus, dyslipidemia, insulin resistance, hypertension and sleep disorders as sleep apnea (8–12). It has been reported that how much more severe obesity is, the higher the risk of low HDL-cholesterol level, high systolic and diastolic blood pressure, high glycated hemoglobin and high triglyceride levels in children and young adults (13).

Obesity is a multifactorial disease; many factors are involved in its development such as genetic, behavioral and environmental risk factors (1,14–16). Factors like pre- and perinatal factors, the family background, laws and policies, cultural norms, food marketing and the local environment are described as key factors to childhood obesity (17). From an ecological perspective, there are six groups on which we can divide the multiple determinants of childhood obesity: the first group includes the more distal determinants such as the society, the norms and public policies; the second group includes social capital, social norms, foodscape, neighborhood, walkability, recreational and sports facilities and air pollution; the third group includes food and physical activity environments and kindergarten or school; the fourth group includes family and socio-economic status; the fifth group includes the child's characteristics; and the last group is composed by the genes (15).

Nowadays is believed that the genetic burden and environmental influences play a major role on the development of obesity (1,14,18). In fact, the rapid population demographic shift towards a more obese phenotype cannot be largely explained by genetic influences nor environmental influences in isolation, but it is believed that the

environment can interact with genes and enhance the predisposition to obesity. Thus, epigenetic mechanisms have been described and the current obesity levels have been linked to gene-environment interactions (18). The gene-environment interactions could be defined by estimating whether the degree of risk attributable to the joint effects of a genotype and an environmental factor in a given outcome is greater or less than would be expected if these joint effects were additive (19).

During the last decade, research has tried to understand the gene(s) responsible for the predisposition for developing obesity during childhood, so many studies were conducted such as family studies, genome-wide linkage studies (GWLS), and more recently genome-wide association studies (GWAS) (20). Childhood obesity could result from the presence of risk genes, such as the fat mass and obesity-associated (FTO) gene, and their response to obesogenic environments (21). The obesogenic environment can be summed up into three major domains, namely access to equipment for exercise, transportation such as access to walking or cycling paths, and availability of healthy and unhealthy foods (15,22).

This review aims to understand how genetic and environmental interactions can predispose to obesity. It will be focused on gene-diet interactions on childhood obesity.

2. Methods

A literature search was conducted to understand how genes and dietary factors can interact and influence the development of childhood obesity. The PubMed Central® search engine was used to retrieve related manuscripts as it represents the more comprehensive dataset for biomedical literature. The following MeSH terms were used: “gene”, “genetic”, “obesity”, “diet”, “child” and “pediatric obesity”. For the purpose of this article, those that seemed relevant to this topic were included, totaling 110 papers; the literature search had three stages, the search for the titles, then the abstracts and finally the full paper was search and retrieved (when deemed of interest). Papers written in English language were included.

3. Childhood Obesity

Definition and Epidemiology

According to the World Health Organization (WHO), childhood obesity is defined as an abnormal or excessive body fat accumulation, enough to cause adverse health effects (23). Overweight and obesity definitions are often based on body mass index (BMI) that is calculated by body mass measured in kilograms divided by the square of the height measured in meters (kg/m^2) (24). In children, BMI requires adjustment for age and gender. WHO standards to children considers a child or infant overweight when is between >2 standard deviations (SD) and ≤ 3 SD of the median in weight-for-length or weight-for-height or BMI-age (2–4,24,25). A child is obese when weight-for-length or weight-for-height or BMI-age is >3 SD of the median (24,25).

The high prevalence of overweight and obesity in several countries has been described as a global pandemic (26,27). In fact, the rates of overweight and obesity are massive all around the world (2–4). As the rates in adults, the prevalence of obesity in children is escalating around the world (2,4). Ng, M. *et al.* in 2014 had reported that between 1980 and 2013 the united prevalence of overweight and obesity among children had a raise of 47,1% (2). In 40 years, the global increase of BMI for girls was $1,28 \text{ kg}/\text{m}^2$ and for boys was $1,40 \text{ kg}/\text{m}^2$ leading to an identical age-standardized BMI for girls and boys, $18,5 \text{ kg}/\text{m}^2$ and $18,6 \text{ kg}/\text{m}^2$, respectively (4). According to the WHO, in 2016, 41 million children under 5 years of age and 340 million children and adolescents (5-19 years old) had overweight or obesity worldwide (24). This scenario is described for both developed countries, where the prevalence of childhood overweight and obesity in 2013 was 23,8% and 22,6% for boys and girls, respectively, and also for developing countries, although in a lower magnitude (12,9% for boys and 13,4% for girls) (2). The scenario in Portugal is also alarming. According to the latest data of the National Food, Nutrition and Physical Activity Survey, conducted in a representative sample of the Portuguese general population during 2015-2016, 22,3% of the Portuguese have obesity and 34,8% have overweight (28). Among children the burden is also high: 7,7% of children under 10 years old have obesity, and the prevalence of overweight children reached 17,3% (28). Nonetheless, the prevalence of childhood obesity in the United States and in some European countries, such as Portugal has apparently reached a plateau (5), but it continues in high rates.

Etiology

Having an excess of weight during growth has, according to Bouchard, three possible explanations (21). The first one is that being overweight or obese as a child develops a major risk of these two conditions as an adult. The second one is related to the correlation of excess of weight being a child and the development of diabetes, cardiovascular disease and other co-morbidities. The third reason is that overweight and obesity as a child could determine the appearance of visceral obesity and even ectopic fat deposition as an adult (21). The rising rates of obesity can also be explained by the availability of high-calorie foods concerted with a sedentary lifestyle (15,29). The social matters such as the family socioeconomic position, the family demographics, characteristics and behaviors and also the children's behavior can lead to overweight or obesity (30). The family context seems to be one of the major determinants of the child's growth. The family context includes some aspects like parental behaviors such as the style of parenting, parenting child-feeding practices and parental diet that will affect indirectly the child's diet (30,31). Still according to the same authors, obesity has numerous aspects that can be considered in the group of social determinants, such as socioeconomic status, health literacy and education, access to health care, residence and work conditions and social support (30). Some factors such as low and adequate weight at birth and parental weight status at the age of 5 years old of the child predict the risk of obesity in adulthood (30).

Childhood obesity should be prevented by intervening at different ecological levels: educating healthy dietary patterns from early life and the communities in which children are engaged, giving recommendations from health professionals to children avoid the consumption of nutrient-poor, calorie-dense foods, promoting physical activity and environments enhancing their practice (8). The obesogenic environment can be summed up into three major domains, namely access to equipment for exercise, transportation such as access to walking or cycling paths, and availability of healthy or unhealthy food (15,22).

Related Consequences

The obesity epidemic comes often followed by high rates of other diseases like type 2 diabetes, cardiovascular diseases (CVD) and cancer (6). In fact, obesity has several co-morbidities and complications in many fields such as cardiovascular (cardiomyopathy and stroke), respiratory (obstructive sleep apnea and higher risk to respiratory infections), gastrointestinal (cholecystitis and reflux esophagitis), cancer (influence on eleven types), orthopedic (osteoarthritis), metabolic (insulin resistance, hyperinsulinemia), reproductive (anovulation in woman and hypogonadotropic hypogonadism in men), obstetric and perinatal (pregnancy-related hypertension), psychologic (isolation and depression) and others affecting the daily life like difficulties in personal hygiene and a decrease in mobility (6,7). The worldwide increase in the prevalence of childhood obesity led also to the appearance of similar illnesses and risk factors at a younger age that would be observed in the past only among adults (9). Childhood overweight and obesity is now associated with type 2 diabetes mellitus, dyslipidemia, insulin resistance, hypertension and sleep disorders as sleep apnea (8–12,32). It has been reported that how much more severe obesity is, the higher the risk of low HDL-cholesterol level, high systolic and diastolic blood pressure, high glycated hemoglobin and high triglyceride levels in children and young adults (13). Psychological and emotional well-being consequences are also worthy to highlight as children with obesity are more likely to report anxiety, depression, and poor self-esteem (33).

4. Genetics of Obesity

Currently, 146 genetic variants are identified associated with BMI (34). It is suggested that having a first-degree relative (mother, father, brother or sister) with a BMI around 40 kg/m² increases in five times the risk of a child be obese than a child with normal-weight (from 18,5 kg/m² to 24,9 kg/m²) first-degree relatives (21,35). Family and adoption studies have also provided evidence that the BMI of an adopted children is strongly correlated with biological first relatives and only have a weak correlation with the BMI of adoptive parents (36,37). Parental overweight, an in particular maternal overweight, can be a risk factor for overweight in childhood, and this can be led by nutrition, lifestyle and genetics (38). Thus, heritability seems to have

an important role in the development of childhood obesity (39,40). Nonetheless, it is also important to highlight that although recent GWAS have identified many loci related to obesity or body mass index, the identified variants explain only a small proportion of the heritability of obesity (1).

Genetics can cause obesity, generally, in three kind of ways: i) by a single gene mutation that is a monogenic cause (gene variants of major effect); ii) by association with phenotypes such as neurodevelopmental abnormalities as in syndromic obesity; iii) by developing a polygenic obesity, which means that the obesity is caused by the contribution of various genes and their effect is intensified by the environment (14). The monogenic abnormalities include LEP mutations and MC4R deficiencies (14). There are identified two major types of disorders: the Mendelian disorders that origin innumerable clinical features including obesity like the Prader-Willi syndrome and the Bardet-Biedl syndrome, and also the monogenic disorders in which the genes of LEP, LEP receptor, pro-opiomelanocortin (POMC), MC4R and prohormone convertase 1 (PCSK1) were highlighted (21,41). Common forms of obesity (the most frequent scenario) are caused by a combination of environmental factors with many gene variants of minor effect (20).

A genetic influence in BMI seems to exist from early ages to childhood (42,43). Nowadays, whole genome and whole exome sequencing are important diagnostic tools to identify new genes and variants associated with (severe) obesity (44,45). There are many genetic factors that can contribute to childhood obesity like the fat mass and obesity-associated (FTO) gene, the leptin (LEP) gene, the melanocortin 4 receptor (MC4R) gene, the ectoenzyme nucleotide pyrophosphate phosphodiesterase 1 (ENPP1) and others like the peroxisome proliferator-activated receptor gamma (PPARG), angiotensin-converting enzyme (ACE) gene and the glutathione S-transferase (GST) gene (14,42,46–49). In general, these variants disrupt enzymes and receptors playing an important role in homeostasis, resulting in endocrine dysfunctions and an early onset of obesity (20).

The FTO gene and its relation with obesity development is probably the most often described in the literature. The expression of the FTO gene occurs in the hypothalamus, being responsible for appetite behavior, fatty acids metabolism and reward driven consumption (46,50,51). The exact function of the protein encoded by this gene is not fully understood, however there is some evidence that attributes it an

important role in energy homeostasis (44). There are proof that mutations in this gene are positively associated to the risk of overweight and obesity and are related to the tendency to consume higher fat content (52). The FTO mutations can also be associated to obesity-related complications such as high blood pressure, plasma insulin levels, insulin resistance and percentage of body fat mass (53). The ethnicity could play a role on the polymorphism of the FTO gene because in African-American children no association was found while on some European and Chinese children an association with diet preference and risk of overweight and obesity has been found (54,55).

MC4R gene regulates satiety which means that plays a major role in food consumption, body weight and energy homeostasis (56). The protein encoded by this gene has the function of controlling satiety and energy expenditure (57,58). Some mutations in the MC4R gene have been associated with obesity in Asian and European populations, both in children, adolescents and adults (59–61). The MC4R gene contributes to an early onset of obesity and it is associated with increased appetite, fasting hyperinsulinemia, incompletely suppressed growth hormone secretion and hyperphagia (57,58,62). Children with deficiencies in MC4R gene are reported to be taller, more obese and with a higher bone mineral density (63,64). MC4R deficiencies can also be associated with an increase of fat mass (65). Both mutations in FTO gene and MC4R gene have an influence on the trajectory of BMI in children (48).

LEP gene expresses a protein that stimulates anorexigenic pathway and in other hand inhibits the orexigenic pathway (66). LEP gene deficiency can lead to insulin resistance and dyslipidemia (20,66). Both LEP and LEP receptor mutated genes could have an early influence on obesity onset and have the same associated traits such as hyperphagia, hypogonadotropic hypogonadism, frequent infections, and some evidence for dysfunction of metabolism have been described; they could also have associated some other clinical characteristics such as short stature, emotional lability and social disability (8,67). Children with mutations on LEP and LEP receptor genes present accelerated weight gain in the first year of their life and are intolerant when dietary restrictions are imposed (68).

POMC is a propeptide expressed in hypothalamus and develops melanocortin peptides such as adrenocorticotrophic hormone and some melanocyte stimulating hormones; these peptides have a key role in energy balance (69). Mutations in POMC gene are reported to have a role in obesity early-onset and adrenal insufficiency (69,70).

POMC deficiency is reported to be a cause of neonatal hypoglycemia and cholestatic jaundice or adrenal crisis related to adrenocorticotrophic hormone deficiency (71).

SH2 B adaptor protein 1 (SH2B1) encodes a cytoplasmatic adaptor protein that modules signaling of LEP-melanocortin and variances in this gene are associated with obesity, insulin resistance and anomalies in behavior such as social isolation and aggressive behavior (72).

5. Gene-Diet Interactions

Gene-diet interactions are characterized by the modulation of the effect of a diet component on a given phenotype (73). From an epidemiological point of view, interaction is defined by estimating whether the degree of risk attributable to the joint effects of a genotype and an environmental factor (like diet) in a given outcome (like obesity) is greater or less than would be expected if these joint effects were additive (19).

Environment englobes a large number of conditions, but the most important are the dietary habits because everyone is exposed to it since birth (73). Nutritional genomics includes nutrigenomics and nutrigenetics (1). Nutrigenomics explores the effects of nutrients or other components of diet on the gene expression, DNA methylation, proteome and metabolome (74). Nutrigenetics aims to understand whether genetic variations modify the relationships between dietary factors and risk of illness (75). Both domains try to further understand the gene-diet interactions, although they have different approaches (76).

Nutrients can affect the genome stability, RNA expression and/or protein expression, which means that diet can affect all the processes that are involved in cells function. In other words, diet can influence the gene expression process and affect different metabolic pathways that finally will origin the phenotype (77). The different diets can influence the genes expression and intensify the development of chronic diseases (73,76). However it is believed that environmental changes can be key triggers in genetics, so it seems possible to prevent obesity development with dietary interventions in individuals that have genetic predisposition for obesity (39,40,46,78).

There are three genes (FTO, MC4R and Niemann-Pick C1 (NPC1)) that promote childhood obesity by interacting with a high-fat diet (79). It is reported that the apolipoprotein A-2 (APOA2) gene is not related to childhood obesity but nowadays represents the best-known gene-diet interaction on the increase of weight gain (80).

The encoded FTO protein catalyzes demethylation of some nucleic acid bases and the FTO gene is regulated by fasting and feeding cycles, which means that it has a role in maintaining energy balance (50,81). There is a variant of the FTO gene that in association with a BMI ≥ 25 kg/m² promotes brain insulin resistance that is implicated in satiety and appetite control having a significant impact in maintaining energy balance (50,81). As reported by López-Bermejo et.al., the presence of the FTO gene in newborns is associated with both fat mass and abdominal fat at two weeks of age in that population (82). It is reported that children and adolescents that have the variant of the FTO gene consume a greater amount of calories from fat, although the energy consumed not being different from the control group (52). The individuals with this variant of the FTO gene seem to have a preference for foods enriched with fat and have decreased satiety, and both these aspects are related to weight gain and development of childhood obesity (52). A mutation in the FTO gene was found to have a positive association for overweight and obesity when the percentage of energy intake that comes from protein is above 12,70% (83). Another variant of the FTO gene was found to be positively associated with fat intake and promote overweight and obesity in children between 4 and 11 years old (83).

An important message is that a dietary intervention combined with exercise can decline the levels of BMI, triglycerides, total cholesterol and insulin levels in children and adolescents that present the FTO gene mutation (84), meaning that genes are not deterministic, they can be modulated by the environment.

The MC4R gene is associated with the POMC gene and the loss of function of them contributes to weight gain and obesity, namely the MC4R is responsible for the most usual patterns of childhood and adult obesity (85,86). The MC4R have three types of variants in which are included more than hundred loss-of-function mutations that are responsible for promoting weight gain and leading to obesity; two mutations that are reported as being protective of obesity by gain-of-function and a intergenic polymorphism that is associated with a moderate risk for obesity (87). It is reported that individuals with MC4R gene variant have a larger waist size circumference and also

tend to have higher consumptions of food and also preference for foods with high content of total and saturated fat (88). Secretion of insulin and leptin are directly associated with the amount of adipose tissue and have an indirect role on the maintenance of energy balance through MC4R pathway by stimulating synthesis of POMC from POMC neurons (86). The variant of MC4R gene can also decrease satiety which means that promote weight gain and childhood obesity (89).

The NPC1 gene is regulated by the sterol regulatory element-binding protein pathway with a role in maintaining homeostasis (cellular, tissue and lipid) (90,91). NPC1 gene seems to have a role promoting obesity early onset (79). NPC1 gene encodes a transmembrane protein that interacts with low-density lipoprotein (LDL) derived cholesterol enriched late endosomes and/or lysosomes (92). The NPC1 protein also facilitates the transport of cholesterol and possibly fatty acids to various cellular compartments (90,92,93). It is reported that the NPC1 gene is associated with morbid obesity in European individuals whether in childhood or adulthood (85).

A cohort study involving 1211 children and adolescents aged 4–11 years evaluated the modifying effect of dietary intake on the association between the LEPR gene and excess weight (94). An interaction between a variant of LEP receptor gene and the intake of daily soft drinks or artificial juices above the median are found to be positively associated with overweight, obesity, and waist circumference. There was also found a positive association between the daily consumption of refined cereal above the median and another variant in LEP receptor gene that can cause overweight and obesity in children between 4 and 11 years old (94). The authors have concluded that the association between the LEP receptor gene and excess weight can be modulated by the type and distribution of dietary fatty acids, sugary drinks, and refined cereals.

APOA2 gene is contained in the alipoprotein multigene family that have a large range of complex physiological functions that are still unknown (95,96). APOA2 have a fundamental role in the regulation of the metabolism of fatty acids and triacylglycerol metabolism modulating the lipoprotein lipase-mediated hydrolysis of triacylglycerol (97). APOA2 regulates adiposity and body weight by the interaction of the gene with a high-fat diet, besides that the protein encoded by APOA2 gene is related to satiety and appetite control (80). Homozygous APOA2 is reported to have an interaction between the mutated gene and the intake of saturated fat that led to an increase in BMI in white

and Hispanic individuals (96). Homozygous APOA2 individuals are also related to the intake of saturated fats which leads to an increase in BMI (98).

In childhood obesity, it has been also reported an interaction between sodium intake and salt-sensitive genes, neural precursor cell expressed developmentally downregulated 4 like (NEDD4L) and cytochrome P450 family 11-subfamily β -2, -aldosterone synthase (CYP11 β 2) in children aged 9 (99). NEDD4L gene expresses a protein that regulates the cell surface of epithelial amiloride-sensitive Na channel (ENaC) and the rate of Na reabsorption in the distal nephron (100). The activity of ENaC seems to have a role in the vascular remodeling in obesity (101). The regulators of aldosterone synthesis are a candidate to explain the relation between obesity and CYP11 β 2, because hyperaldosteronism has been related to insulin resistance and fat accumulation (99,102).

SH2B1, potassium channel tetramerization domain containing 15 (KCTD15), neuronal growth regulator 1 (NEGR1) genes mutations were associated with intakes of total, saturated and monounsaturated fat (88). KCTD15 and mitochondrial carrier 2 (MTCH2) mutation genes are associated with the intakes of total carbohydrates, monosaccharide, disaccharide and polysaccharide (88), however these associations were not reported in children.

6. Discussion

Strengths and Limitations of Genome-Wide Association Studies

GWAS have allowed unexpected findings such as the finding of the innumerable number of loci of genes prompting weight gains (44,48). In general, GWAS have led to a better understanding of genes and their architecture towards obesity and also led to find that most locus have a very small contribution to a complex disease (44). GWAS are an important tool to assess chromosome regions that present predisposition to obesity (34,44).

On the other hand, the GWAS come up with many limitations related with the shape of the body and the use of BMI as a measurement tool (103). Issues about masses (organ and tissues), constant change of height and weight, and difficulties on the control

of body weight indicates that future GWAS maybe should be focused on a weight change phenotype (103). In general, the GWAS present publication bias, have low sample sizes, most of the findings are based on observational studies and the validity and accuracy of dietary measurement have been discussed (1,104). Efforts have been done to have larger data on GWAS studies to be able to find out loci that are implicated in obesity (44).

In general, despite some progress in characterizing gene-diet interactions underlying obesity, many challenges remain.

Future Research

To further understand the etiology of obesity and the expression of genes and their association with environments is important to do more research in gene-environmental studies by including other domains like metabolomics and transcriptomics, and having information about the genetic influences in body composition from a life course approach (1,42,105). It is important to figure out how genes can affect the weight gain in childhood, to understand how many more genes can possibly be affecting this weight gain and also this pattern should be studied by genetic profile scores or multiple genes (106). Larger meta-analyses and the use of whole-genome sequences could be a new approach to discover more rare variants that could cause small effects (29,107).

There is the need that GWAS include factors like different environments and their interaction with the genes found to have an implication in obesity, and larger samples for that analyzes (44). In addition, best questionnaires and measurement approaches should be used in the evaluation of obesity and diet, because food-frequency questionnaires have limitations of reliability and validity (108). Researchers believe that besides GWAS further gene-environmental studies are needed to help understanding disease mechanisms (1). To further understand gene-diet interactions it is need that all sequencing of genome is known (73). There are new strategies that led to a precise and faster screening, that grant the identification of mutations in genes and by that a personalized treatment can be done, resulting in a better life for the individual (109). In fact, new personalized therapeutic targets against obesity have been searched. In the near future, individuals may be able to obtain their comprehensive genetic information

and get knowledge of their genetic predisposition to obesity and other chronic diseases (1). Screening programs could identify children at genetic high-risk and then provide them dietary interventions and proper lifestyle changes to prevent weight gain and obesity (46). It is important to have an interdisciplinary approach in order to promote prevention, management and treatment strategies to genetic risk individuals and populations (110). However, the usefulness of a genetic diagnostic approach, in order to identify high-risk individuals for more efficient and targeted diet and/or lifestyle interventions should be further discussed as dietary interventions and lifestyle changes proposals would probably benefit the whole population.

7. Conclusions

GWAS have identified many loci related to obesity or weight gain, however the identified variants explain only a small fraction of the heritability of obesity. In most cases, the individual variability for developing obesity is due to many gene variants of minor effects. The interaction between these gene variants and the environment intensifies the risk for developing obesity since early ages. Thus, genes are not deterministic, they can be modulated by the environment. Several gene-diet interactions have been described in childhood obesity, mostly related with dietary fat intake, and affecting the fatty acids metabolism, so to further understand other metabolic pathways further studies are needed.

A better understanding of the interplay between genetic and environmental factors is the basis for developing effective personalized obesity prevention and management strategies. It is believed that the approach to childhood obesity prevention should be changed from an one-size-fits all to interventions that are focused on populations that are genetically vulnerable. Currently, personalized nutritional and/or medical therapy are in discussion to fight against childhood obesity.

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