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Adiponectin gene polymorphisms: Association with childhood obesity

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Abstract. The current childhood obesity epidemic represents a particular challenge for public health. Understanding of the etiological mechanisms of obesity remains integral in treating this complex disorder. In recent years, studies have elucidated the influence of hormones secreted by adipose tissue named adipokines. Adiponectin is a adipokine that exhibits important anti-inflammatory, insulin-sensitizing and anti-atherogenic properties and it is strongly associated to obesity development. It is well known that adiponectin levels decrease with obesity. Furthermore, studies show that some single nucleotide polymorphisms in the gene encoding adiponectin, *ADIPOQ*, may influence the expression of this protein. The objective of this paper is to provide an up-to-date review of *ADIPOQ* polymorphisms in the context of childhood obesity.

Keywords: Adiponectin, adipokines, childhood obesity, polymorphisms

1. Introduction

Childhood obesity is a significant challenge to global public health in the 21st century. Current estimates show that, worldwide, over 43 million children are overweight or obese [1]. The prevalence of overweight and obese children had increased from 4.2% in 1990 to 6.7% in 2010 worldwide and is expected to reach 9.1%, or about 60 million in 2020 [2]. According to World Health Organization, in 2012 the prevalence of overweight children varies from 6.4% in Africa to 12.1% in Europe [3]. In USA, the prevalence of obese and overweight children and adolescents reaches 31.8% [4]. It is known that overweight and obesity are risk factors for several complications for life, such as cardiovascular diseases [5–7], metabolic syndrome [8–10], type 2 diabetes mellitus [11, 12] and dyslipidemia [12–14], including those occurring in childhood.

In order to reduce the prevalence of obesity, its underlying etiology must be well understood. Sedentary behavior and high calorie diets are certainly important as environmental risk factors. However, it is also necessary to understand the role of predisposing factors, such as genetic and epigenetic mechanisms. Family studies have demonstrated the influence of genes on the occurrence of obesity, and today at least 52 genetic loci are associated with obesity-related traits [15]. However, little is known about the genetic basis of obesity in the pediatric population. Thus, the current understanding is that pediatric obesity largely corresponds to a complex phenotype modulated by gene-environment interactions that influence health in adulthood [16].

For many years, it was believed that adipose tissue was mainly for lipid storage, mechanical protection and thermal balance of the body. However, numerous studies throughout the last several decades have

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shown that adipose tissue is, in fact, a multi-potential secretory organ [17] (Fig. 1). In the mid-1990s, leptin, a hormonal satiety signal, was discovered to be secreted from adipose tissue. To date, numerous other endocrine-active signaling molecules (adipokines) have been isolated [18], including adiponectin, resistin, vaspin, visfatin, interleukin-6 and tumor necrosis factor alpha [19]. The adipokines or adipocytokines term refers to a wide range of adipose tissue-derived factors that have various actions including regulation of carbohydrate and lipid metabolism, insulin sensitivity and regulation of feeding behavior including hunger and satiety.

Adiponectin is a regulator of glucose and lipid metabolism, increasing insulin sensitivity, fatty acids oxidation and glucose tolerance, exhibiting anti-inflammatory and antiatherogenic effects [20, 21]. It is well known that adiponectin levels are inversely related to adipocyte hypertrophy and higher levels of body fat in adults [22]. Lower adiponectin levels are strongly associated with overweight, obesity, metabolic syndrome, type 2 diabetes mellitus and cardiovascular risk factors in adulthood [22–25]. In children and adolescents, hypoadiponectinemia have been shown to predict obesity, metabolic syndrome, hypertension, insulin resistance and visceral fat accumulation [26–31]. Furthermore, studies have shown that some single nucleotide polymorphisms (SNPs) in the gene encoding adiponectin, *ADIPOQ*, may influence the expression of this protein (32–37).

The objective of this work was to describe studies regarding the polymorphisms in the adiponectin gene in the context of childhood obesity, through gathering data suggesting that variations in this gene can be a risk factor associated with the occurrence of obesity in children.

2. Adiponectin: Definition and actions

Adiponectin was independently discovered and described by four research groups in 1995 and 1996 and was initially named adipocyte complement-related protein of 30 kDa (Acrp30) [38], gelatin binding protein 28 (GPB28) [39], adipose most abundant transcript 1 (apM1) [40] and AdipoQ [41]. It was described in 1995 by Scherer et al. [38] as a novel secretory protein, produced exclusively in adipocytes and structurally similar to complement factor C1q, whose secretion is enhanced by insulin. These authors also mentioned

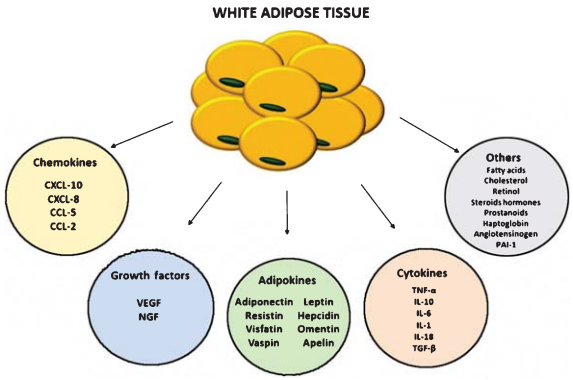

Fig. 1. Major substances secreted by white adipose tissue. CXCL = CXC chemokine ligand; CCL = Chemokine (C-C motif) ligand; VEGF = Vascular endothelial growth factor; NGF = Nerve growth factor; TNF = Tumor necrosis factor, IL = Interleukin; TGF = Transforming growth factor; PAI = Plasminogen activator inhibitor.

that Acrp30 might participate in the balance of energy homeostasis involving food intake, carbohydrate and lipid catabolism.

Adiponectin is a 30 kilo-Daltons (kDa) protein hormone consisting of 244 amino acid residues. The primary sequence of adiponectin comprises a short amino-terminal signal sequence, a species-specific variable region, an N-terminal collagenous domain and a C-terminal globular trimerization [42] (Fig. 2A). The C-terminal adiponectin globular (gAD) is the essential functional portion of the protein and may be released by an enzymatic cleavage mediated by leukocyte-derived elastase [43–47].

Adiponectin is produced as a monomeric protein; however, it circulates in multimeric forms (Fig. 2B) that are formed through post-translational events [48]. The different oligomers of adiponectin include the low molecular weight (trimeric) form, the albumin binding LMW form, the medium molecular weight (hexameric) form and the high molecular weight (oligomeric) form [49, 50]. Adiponectin exerts its functions through two receptors, AdipoR1 and AdipoR2, which were cloned in 2003 [51]. These receptors are present in various tissues but AdipoR1 is abundantly expressed in skeletal muscle and has greater affinity for the adiponectin globular domain, whereas AdipoR2 is predominantly expressed in the liver and exhibits greater affinity for the intact molecule (Fig. 2B) [51, 52]. Adiponectin receptors mediate a wide spectrum of metabolic reactions, including inhibition of gluconeogenesis, glucose uptake and fatty-acid oxidation

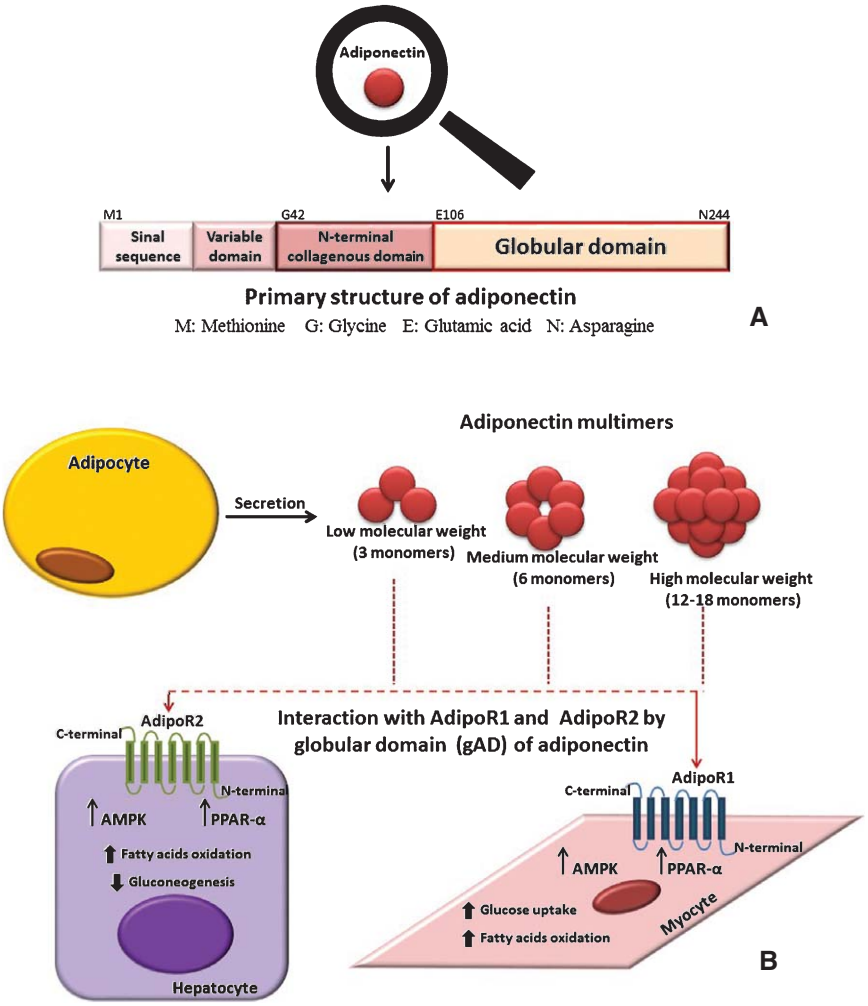

Fig. 2. Adiponectin structure and intracellular signaling. (A) Primary sequence of adiponectin. (B) Adiponectin circulating multimers and receptors, AdipoR1 and AdipoR2: effects on glucose and lipid metabolism in hepatocytes and myocytes.

[53, 54]. Hence, adiponectin is of great importance for metabolic disorders such as obesity, insulin resistance, type 2 diabetes mellitus and dyslipidemia, including the possibility of using this protein as a biomarker and as a potential therapeutic agent for these disorders.

3. Adiponectin gene polymorphisms

The adiponectin gene, *ADIPOQ* was first cloned in 1999, when its structure was first reported. *ADIPOQ* is located on the long arm of chromosome 3 at position 3q27, spanning about 16 kb and contain three exons and two introns [55] (Fig. 3). There are alternative titles for this gene: adipose most abundant gene transcript 1 (*APM1*), gelatin-binding protein, 28 KD (*GBP28*), adiponectin (*ADPN*), adipocyte complement-related protein 30 (*ACRP30*), adipocyte C1q and collagen domain containing (*ACDC*).

Many SNPs have been identified in the human *ADIPOQ* and the SNP database [56] currently contains 813 results. These polymorphisms are distributed throughout the gene structure and their clinical and phenotypic significance is being investigated by ongoing research. Studies have evaluated the role of some of these polymorphisms in several clinical conditions, such: insulin resistance [53, 57], type 2 diabetes mellitus [58–60], gestational diabetes mellitus, gestational hypertension and pre-eclampsia [61–64], obesity [65–67], cardiovascular disorders [68–70],

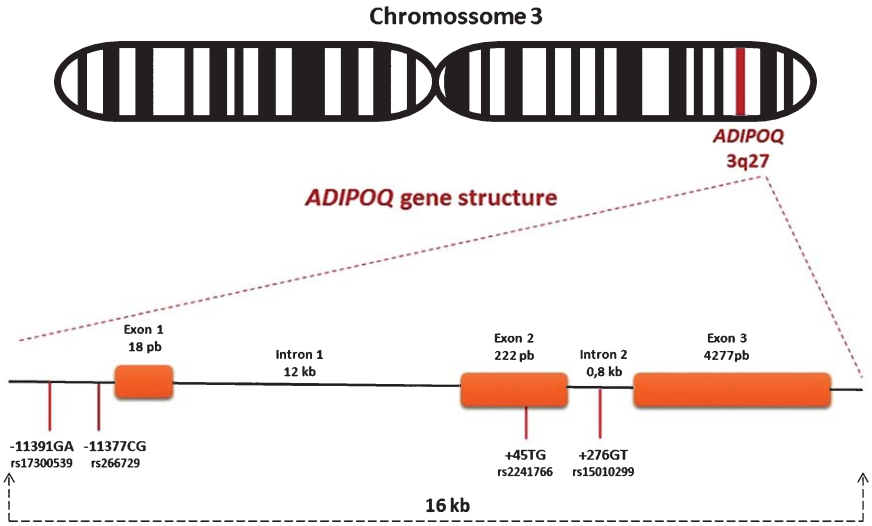

Fig. 3. Location and structure of *ADIPOQ* gene and polymorphisms.

polycystic ovary syndrome [71–73], knee osteoarthritis [74], cancer [75, 76] and non-alcoholic fatty liver disease [77]. The findings reported in these association studies vary by condition and are sometimes contradictory to each other, suggesting the need for further replication. In the context of childhood obesity, four polymorphisms in *ADIPOQ* have been studied, two located in the promoter region of the gene (−11391G>A and −11377C>G), one within exon 2 (+45T>G) and one within intron 2 (+276G>T) (Fig. 3). The phenotypic significance of the polymorphisms within the gene are shown in Table 1.

4. Materials and methods

Different terms in English were used for the systematic search in Pubmed, Cochrane, Science Direct and Scopus database, such: "polymorphisms adiponectin childhood obesity", "polymorphisms adiponectin obese children", "polymorphisms *ADIPOQ* obese children", "polymorphisms *ADIPOQ* childhood obesity", "variants *ADIPOQ* childhood obesity", "variants *ADIPOQ* obese children", "variants adiponectin gene childhood obesity", "variants adiponectin gene obese children". We included in this review articles dealing specifically with respect to *ADIPOQ* variants and childhood obesity, totaling to about 15 works published between 2006 and 2014 (Table 2). No meta-analyses were found addressing the theme. All the studies in English, Spanish or Chinese language were included in the present review.

5. Results

5.1. Adiponectin gene polymorphisms and childhood obesity

In 2006, Bouatia-Naji et al. [32] investigated the role of the *ADIPOQ* SNPs −11377C>G, −11391G>A, +45T>G, and +276G>T in a population of 2,579 French Caucasians including obese adults and children (534 morbidly obese children, 695 morbidly obese adults and 1,350 control subjects). They found an asso-

Table 1
Phenotypic significance of *ADIPOQ* polymorphisms related to childhood obesity

ADIPOQ polymorphism associated with childhood obesity	Phenotypic significance
−11391G>A (rs17300539)	−11391G is associated with lower adiponectin levels [32–34]
−11377C>G (rs266729)	−11377C is associated with higher adiponectin levels [32,33,35]
+45T>G (rs2241766)	+45T is associated with higher adiponectin levels [33]
+276G>T (rs1501299)	+276T is associated with higher adiponectin levels, but this relationship seems to depend of the ethnicity of the population studied [36,37]

ciation between severe forms of obesity and the alleles −11377C and +276T, although these alleles have been associated with higher adiponectin levels in other studies [33, 35, 78]. There was no significant association between −1391G>A or +45T>G and obesity in this study, but the allele −11391A was associated with higher adiponectin levels in obese children than those from the general population. These controversies could be explained by the fact that the odds ratio reported in this study was not adjusted for covariates such as age and gender.

Also, Petrone et al. [33] studied the influence of the same SNPs −11391G>A, −11377C>G, +45T>G, and +276G>T and the haplotypes with the insulin resistance state in 270 overweight/obese children. They found an association between the −11391GG genotype and higher fasting insulin levels and lower adiponectin levels compared with that GA and AA genotypes. Further, they found an association between the −11377G allele and higher fasting glucose, fasting insulin, triglyceride levels and lower adiponectin levels when compared to C homozygotes; and association between +45G allele with higher fasting, 2-hr glucose levels and lower adiponectin levels. Analyzing haplotypes related to childhood obesity, the authors observed that the effect of +45T>G SNP was marginal compared with the promoter SNPs and the presence of the −11391G/ −11377G/ +45T haplotype was associated with the highest degree of insulin resistance (IR).

The polymorphisms −11391G>A and −11377C>G were studied in a population composed of 243 obese children and adolescents from Poland compared to 100 non-obese adults without a history of obesity. Only an association between −11377GG genotype and obesity was found, however, there was no effect of this polymorphism on body mass index (BMI) within obese patients [79].

Verduci et al. [80] analyzed the association between the SNP +276G>T and IR and plasma long-chain polyunsaturated fatty acids in obese Italian children. The sample population consisted of 131 normolipidemic obese children aged 8-13-year-old. The prevalence of the allele +276T in this sample was 48.8% and the carriers presented higher fasting insulin levels and increased insulin resistance when compared to non-carriers. In addition, the +276T carriers showed higher levels of n – 6/n – 3 plasma long-chain polyunsaturated fatty acids ratio and a lower C20:5n – 3/C20:4n – 6 ratio in plasma phospholipids than non-carriers.

The role of the +276G>T SNP was also investigated by Johansson et al. [81] with respect to IR and lipid levels in 285 obese children and adolescents from Sweden. They found no association between this polymorphism and BMI, high-density lipoprotein cholesterol, triglycerides or IR, but concluded that homozygous carriers of the allele +276T had higher total and low-density lipoprotein cholesterol (LDLc) levels adjusted for age, gender, BMI, insulin sensitivity and ApoE genotype.

Panagopoulou et al. [82] analyzed the influence of two SNPs +45T>G and +276G>T on adiponectin levels and IR in 48 obese Greek children and adolescents aged from 3 to 16-year-old. They observed no significant difference in adiponectin levels in subjects with genotype +45TT and +45GG or between individuals with genotypes +276GG and +276 TT. The polymorphism +45T>G was not associated with IR, but the +276G>T was associated with decreased risk of IR.

The same polymorphisms were investigated by Riestra et al. [83] in 815 healthy Spanish children. No difference was observed in the frequencies of the polymorphisms between normal and overweight children. However, overweight male carriers of 276T allele presented lower total cholesterol, LDLc and ApoAI levels. Moreover, an interaction between BMI and +276G>T was observed as a significant predictor of the total cholesterol and LDLc in the same group.

Ntalla et al. [84] investigated the influence of the SNPs −11391G>A and +276G>T on serum adiponectin concentration in response to dietary factors in 991 school-aged children of Greek origin. This study was based on the hypothesis that a diet rich in fiber could decrease adiponectin expression. They observed that with lower fiber intake, +276GG, compared to T carriers, showed higher adiponectin levels and could be protected against the risk of obesity and insulin resistance.

In 2010, Morandi et al. [85] studied the metabolic role of SNP −11391G>A in a large sample of children of European origin totaling 1852 obese and non-obese children. They demonstrated that carriers of the −11391GG genotype had lower circulating levels of adiponectin than individuals with genotypes GA and AA. However, a higher prevalence of obesity in carriers of the A allele was observed. The authors discussed that the state of chronic hyperadiponectinemia associated with the −11391A allele could enhance the risk of childhood obesity by promoting cell proliferation and differentiation from preadipocytes into adipocytes and increasing lipid content.

Table 2
Summary of data on association between *ADIPOQ* polymorphisms and childhood obesity

Publication	Population studied number	ADIPOQ polymorphisms studied	Genotypic frequencies in obese children (%)												Main conclusion
			−11391G>A			−11377C>G			+45T>G			+276G>T			
			GG	GA	AA	CC	CG	GG	TT	TG	GG	GG	GT	TT	
Bouatia-Naji et al. [32]	French (2579)	−11391G>A −11377C>G +45T>G +276G>T	81.5	17.3	1.2	58.4	36.4	5.2	73.2	24.9	1.9	49.8	40.8	9.4	Association between severe forms of obesity and −11377C and +276T
Petrone et al. [33]	Italian (270)	−11391G>A 11377C>G +45T>G +276G>T	81.1	18.2	0.7	54.8	36	9.2	77	21.9	1.1	60	33	18	−11391G, −11377G and +45G are associated with lower adiponectin levels and the haplotype −11391G −11377G +45T is associated with the highest degree of IR
Verduci et al. [80]	Italian (131)	+276G>T	–	–	–	–	–	–	–	–	–	51.2	38.8	9.9	The allele +276T is associated with higher fasting insulin levels, increased IR and higher risk of metabolic complications
Johansson et al. [81]	Swiss (285)	+276G>T	–	–	–	–	–	–	–	–	–	UI	UI	UI	Homozygous carriers of the allele +276T had higher total and LDL-c levels
Panagopoulou et al. [82]	Greek (48)	+45T>G +276G>T	–	–	–	–	–	–	UI	UI	UI	UI	UI	UI	No significant difference in adiponectin levels was observed in subjects with genotype +45TT and +45GG or between individuals with genotypes +276GG and +276 TT. The allele +276T was associated with decreased risk of IR
Ntalla et al. [84]	Greek (991)	−11391G>A +276G>T	UI	UI	UI	–	–	–	–	–	–	UI	UI	UI	With lower fibre intake, +276GG, compared to T carriers, showed higher adiponectin levels
Morandi et al. [85]	European (1852)	−11391G>A	81	18	1	–	–	–	–	–	–	–	–	–	−11391GG genotype had lower circulating levels of adiponectin that individuals with genotypes GA and AA but this finding does not exert any appreciable protective metabolic effect in children
Cieslak et al. [79]	Polish (343)	−11391G>A −11377C>G	86.8	13.2	0	47.8	43.6	8.6	–	–	–	–	–	–	Association between obesity and −11377GG genotype
Wu et al. [86]	Chinese (265)	+45T>G	–	–	–	–	–	–	UI	UI	UI	–	–	–	+45T>G may be associated an increased risk of childhood obesity and results in a decreased level of adiponectin.
Orellana et al. [87]	Chilean (367)	−11391G>A −11377C>G +45T>G +276G>T	78	21	0	75	6	19	66	16	18	75	26	0	The allele −11377G is associated with increased risk of childhood obesity

Table 2
(*Continued*)

Publication	Population studied number	ADIPOQ polymorphisms studied	Genotypic frequencies in obese children (%)												Main conclusion
			−11391G>A			−11377C>G			+45T>G			+276G>T			
			GG	GA	AA	CC	CG	GG	TT	TG	GG	GG	GT	TT	
Cieslak et al. [88]	Polish (53)	−11377C>G	–	–	–	60.3	31.3	8.4	–	–	–	–	–	–	No significant association between genotype and adiponectin gene expression
Riestra et al. [83]	Spanish (815)	+45T>G +276G>T	–	–	–	–	–	–	–	UI	UI	UI	UI	UI	Interaction between 276T allele and BMI predictors of the total cholesterol and LDLc
Léon-Mimila et al. [89]	Mexican (1218)	+45T>G	–	–	–	–	–	–	UI	UI	UI	–	–	–	Significant associations with obesity and SNP +45T>G for adults but the same finding did not repeat among children
Galcheva et al. [90]	Bulgarian (168)	+45T>G +276G>T	–	–	–	–	–	–	UI	UI	UI	UI	UI	UI	Individuals with +276T allele expressed higher obesity-related measures and lower adiponectin concentrations and carriers of +45GG genotype showed worse obesity measures, and lower serum adiponectin values
Park et al. [91]	Korean (135)	−11377C>G +45T>G +276G>T	–	–	–	UI	UI	UI	UI	UI	UI	UI	UI	UI	−11377G allele carriers had significantly higher serum total cholesterol and LDL-c compared to non-carriers. The haplotype −11377G/ +45T / +276G had higher levels of total cholesterol and LDLc

UI = Uninformed or inaccessible; IR = Insulin resistance; LDLc = Low-density lipoprotein cholesterol; BMI = Body mass index.

Wu et al. [86] investigated the frequency of the SNP +45T>G in Chinese children using a sample of 147 obese and 118 healthy children. They found higher prevalence of this polymorphism in obese children compared to non-obese children (40.5% and 25.4%, respectively). The plasma adiponectin levels were significantly higher in obese children with TT genotype than those with TG or GG genotype. The authors concluded that +45T>G SNP may be associated with an increased risk of childhood obesity and results in a decreased level of adiponectin.

A relationship between adiponectin SNPs −11377C>G, −11391G>A, +45T>G, and +276G>T and childhood obesity in a Chilean children was conducted by Orellana et al. [87]. They used a sample of 241 obese and 126 normal weight children. They showed a higher frequency of the −11377G allele in obese children compared with controls.

Also in 2012, Cieslak et al. [88] studied the influence of SNP −11377C>G on adiponectin gene expression in 53 blood and subcutaneous adipose tissue samples from 48 obese and 5 non-obese children and adolescents of Polish origin. The polymorphism did not modify significantly the expression of adiponectin gene, suggesting that this SNP is not a good marker for predisposition to obesity in Polish children.

In 2013, León-Mimila et al. [89] investigated the role of polymorphisms in many genes associated with obesity in Mexican children and adults, including the *ADIPOQ* polymorphism +45T>G. The sample in this study included 1218 children. They found significant associations with obesity and SNP +45T>G for adults after adjusting for age, sex and admixture, but the same finding did not repeat among children.

Galcheva et al. [90] examined the influence of SNPs +276G>T and +45T>G on adiponectin levels in prepubertal children with and without abdominal obesity to evaluate their relationship with adiposity and cardiometabolic risk factors. The sample included 168 children aged from 6 to 10-year-old divided in groups based on waist circumference. It was observed that individuals with +276T allele expressed higher obesity-related measures and lower adiponectin concentrations and carriers of +45GG genotype showed worse obesity measures, higher triglyceride, glucose and insulin and lower serum adiponectin values when compared to the +45T allele carriers.

Finally, in 2014, Park et al. [91] investigated the relationship between SNPs −11377C>G, +45T>G, and +276G>T and serum lipids levels in 687 (552 with normal weight and 135 with overweight) Korean children aged 7-11-year-old and whether those influences might be modulated by dietary factors such as dietary monounsaturated fatty acid to saturated fatty acid ratio. The −11377G allele carriers had significantly higher serum total cholesterol and LDL-c when compared to non-carriers. A haplotype analysis showed that carriers of −11377G/ +45T/ +276G also presented higher levels of total cholesterol and LDL-c when compared with non-carriers, but this deleterious effect only happened when the MUFA:SFA ratio was <1.

Several studies evaluating the polymorphisms in *ADIPOQ* gene and the obesity in adults were conducted, although controversies still exist about this association, similar to those observed in childhood. The same polymorphisms often associated with obesity in children/adolescent are also commonly studied in the context of obesity in adults (rs17300539, rs266729, rs2241766, rs15010299). The findings of these studies are also similar, including: the allele +45G is more common in controls when compared with obese individuals [92] and the +45GG genotype increases obesity risk in the Chinese population but not in the non-Chinese individuals [93]. Moreover, the genotypes −11377GG and −11391GA were positively associated with risk of central obesity [94] and −11391AA genotype was associated with increased BMI [95]. For the SNP +276G>T, the association with obesity also appears to depend on the ethnicity of the population, since the frequency of the allele +276T was significantly higher among the obese subjects compared to the non-obese subjects in an Indian study [96], while the +276 TT genotype was more common in non-obese Tunisian subjects [95].

5.2. *Heritability of plasma adiponectin, quantitative trait loci and obesity*

In an investigation conducted by Zadjali et al. [97] including 383 adults of Arab ancestry, 4.1% of heritability of obesity traits was observed to be explained by the SNP −11377C>G in adiponectin gene.

Heritability estimation in a 1245 Chinese adolescent population aged from 13 to 21 yr showed that both environmental and genetic factors contribute to variance in adiponectin levels [98]. In another study, the adiponectin plasma levels showed a heritability of 55.1% in 2,256 healthy individuals from Netherlands [99].

Tests of heritability with a series of 60 pairs of healthy young twins from Poland and Italy also identified plasma adiponectin levels heritability. In this study, a model of a likelihood-based analysis including an additive genetic influence and an individually unique environmental influence showed association with 88% and 12% of adiponectin levels variance, respectively. Moreover, higher within-pair difference of adiponectin levels was observed in dizygotic than in monozygotic twins [100].

Chung et al. [101] in a study with 382 young Chinese individuals, conducted a genome-wide association study to identify quantitative trait loci associated with high molecular weight forms of adiponectin levels and observed that SNP (rs4783244) located in intron 1 of the T-cadherin (CDH13) gene modulated the adiponectin levels, although the mechanism has not been elucidated. Indeed, Tejero et al. [102], in a study with 466 Hispanic children aged from 4 to 19 yr, identified three new regions on chromosomes 11, 8 and 18 linked to adiponectin levels. All the chromosome regions identified in this study have been linked to obesity and diabetes-related phenotypes in adults across different ethnicities. Finally, fine mapping of these regions is necessary in order to identify genetic polymorphisms that influence the circulating levels of adiponectin.

6. Conclusion

Although inconsistencies in the strengths and directions of *ADIPOQ* gene and obesity are discussed in some studies, it is clear that *ADIPOQ* SNPs, mainly the SNPs −11377C>G, +45T>G +276G>T, are an important part of an individual's predisposition to obesity and various metabolic health outcomes.

Considering that obesity is associated with metabolic complications, this current knowledge implicates that it should be prevented as early as possible. The identification of polymorphisms in the *ADIPOQ* gene could help to prevent this disorder, by changing the life style.

It is still necessary to better understand the phenotypic impact of *ADIPOQ* polymorphisms in populations of different ethnic origins and age groups. Moreover, it remains important to continue examining the gene-environment interaction in order to adopt preventive actions and measure the real impact of these polymorphisms on obesity during childhood.

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