J Pediatr Rev. 2018 January; 6(1):e10536. doi: 10.5812/jpr.10536.

Published online 2017 October 8. **Review Article**

A Systematic Review of Single Nucleotide Polymorphisms Associated With Metabolic Syndrome in Children and Adolescents

Roya Kelishadi,[1] Silva Hovsepian,[1,*] and Shaghayegh Haghjooy Javanmard[2]

[1]Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non Communicable Disease, Isfahan University of Medical Sciences, Isfahan, IR Iran
[2]Department of Physiology, Applied Physiology research Center, Isfahan University of Medical Sciences, Isfahan, Iran

[*]*Corresponding author*: Silva Hovsepian MD, PhD Candidate, Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non Communicable Disease, Isfahan University of Medical Sciences, Hezar-Jerib Ave., P.O. Box: 319, Isfahan, IR Iran. Tel: +98-3137923320-21, Fax: +98-3137923320, E-mail: silvahovsepsecret@gmail.com

Received 2017 January 17; **Revised** 2017 April 17; **Accepted** 2017 May 02.

Abstract

Context: Metabolic syndrome (MetS) is defined as clustering of risk factors including obesity, dyslipidemia, hyperglycemia, and hypertension, which is associated with increased risk of cardiovascular disease (CVD) and Type 2 diabetes mellitus (T2DM).
Objectives: The present study aimed at reviewing all reported single-nucleotide polymorphisms (SNPs) related to childhood metabolic syndrome (MetS).
Data Sources: In this review, an electronic literature search was conducted in PubMed and Huge Navigator database. For the HuGE Navigator search, we used the "metabolic syndrome" search term. For the PubMed search, we used "metabolic syndrome", "child", "adolescents", "pediatrics", "genes", and "polymorphism", without any restriction for time and language.
Study Selection: Human studies with cross-sectional or case-control designs, which contained MetS as outcome and recruited participants younger than 21 years, were included. All definitions of pediatrics MetS were acceptable.
Data Extraction: This study was designed as systematic review without meta-analysis in accordance with the preferred reporting item for systematic reviews meta-analysis (PRISMA) statement recommendation. After excluding duplicated and irrelevant studies, data extraction and quality control were conducted by 2 researchers using STROBE checklist.
Results: In this review, during primary literature search, 219 and 1025 articles were identified through PubMed and HuGE navigator database, respectively. During 2 refining steps and after quality assessment, 38 qualified articles were evaluated at the final step. According to the whole data of systematic review results, the number of total population and points of data were 14 536. Number of studied genes and related SNP were 60 and 125, respectively. SNPs of the following genes were associated with MetS: GCK, HNFAα, SHBG, PON1, adiponectin, obesity related genes (FTO, MC4R, GNPDA2, BDNF, FAIM2, NPC1, SEC16B, SH2B1, PCSK1, KCTD15, and BAT2), PAI, AT1R, and SR-BI. SNPs of the following genes were associated with component of MetS: GCK, ACE, ABCA1, SREBP-1, miR-33b, PAI, IL6R, IL18, TCF7L2, ADRB2, and TNFα. SNPs of the following genes did not have any association with MetS or its components: CRP, APOA5, PPARγ, PGC-1γ, Tfam.
Conclusions: The findings of this review revealed that most reported SNPs are related to lipid disorders mainly triglyceride and HDL and insulin resistance. It is suggested that combination effect of most of the reported SNPs or their interaction with environmental factors would be more effective for development of MetS in children.

Keywords: Metabolic Syndrome, Child, Adolescents, Polymorphism, Genes

1. Context

Metabolic syndrome (MetS) is defined as clustering of risk factors including obesity, dyslipidemia, hyperglycemia, and hypertension, which is associated with increased risk of cardiovascular disease (CVD) and Type 2 diabetes mellitus (T2DM)) (1). Although MetS was primarily defined as an adult disorder, evidences indicated that during the last decades it has reached to epidemic proportions worldwide in the pediatric population (2, 3).

Prevalence of MetS in children and adolescents has been reported to be 3.3%, ranging from 0% to 19.2% in different populations (4).

The current understanding of MetS indicated that it is a polygenic disease, which could be influenced by different environmental factors. Interactions between different environmental factors and inherited single specific risk alleles may result in development of MetS (5). On the other hand, recent studies indicated that additive effect of differ-

ent risk alleles related to the component of MetS could be more effective in the development of MetS (6).

Previous studies demonstrated that MetS could be heritable in 10% to 30% of the cases (7). In addition, evidences showed the early life origin of MetS (8).

Several SNPs underlying MetS development in pediatric population have been reported, but the results are inconsistent (9-15) (16-25) (26-36) (37-46). There is not any comprehensive report about different reported risk alleles of MetS in children and adolescents. It is suggested that providing an overview from the available evidences of MetS related SNPs could be helpful in understanding the genomics of MetS and that integrations of both clinical and biological information would help us in better management of the disorder and implementation of genetic base treatment.

2. Objectives

This review aimed at reviewing all reported SNPs related to childhood MetS. Our findings provide us with baseline information for future genetic studies as well as current information for planning more effective management plans for this group of population, which consequently could decrease the burden of the disease and its related long- term consequences.

3. Data Sources

This study was designed as a systematic review without meta-analysis in accordance with the preferred reporting item for systematic reviews meta-analysis (PRISMA) statement recommendation for reviewing all reported SNPs related to childhood MetS.

In this review, an electronic literature search was conducted in PubMed and HuGE Navigator database.

The results of population-based epidemiologic studies of human genes since 2001 were extracted from PubMed and HuGE navigator database. Evidences indicated that HuGE Navigator has similar sensitivity but more specificity than PubMed database (47).

Considering that this database retrieved published papers since 2001, we conducted an additional search from PubMed central for all studies published up to April 2016 without any restriction for time and language.

For the HuGE Navigator search, we used the "metabolic syndrome" search term.

For the PubMed search, we used "metabolic syndrome", "child", "adolescents", "pediatrics", "genes", and "polymorphism" terms and the following strategy: ["metabolic syndrome"AND "child" OR "adolescents" OR "pediatrics" AND "genes" OR "polymorphism"].

The latest search was conducted on April 5th, 2016.

Human studies with cross-sectional or case-control designs, which contained MetS as outcome and recruited participants younger than 21 years, were included in the review. All definitions of pediatrics MetS were acceptable.

4. Study Selection and Data Extraction

First step selection was based on title and abstracts. A list of studies was performed accordingly. The full text of the studies were provided and reviewed based on inclusion and exclusion criteria for eligibility. After excluding duplicated studies, the full texts of articles were carefully studied by 2 researchers. The related articles were selected and the irrelevant ones were excluded. Quality of the studies was evaluated by the 2 researchers independently based on the characteristics of the studies and strengthening the reporting of observational studies in epidemiology (STROBE) checklist. Disagreements were resolved by consensus and mutual discussion.

For each finally included article, the following information was extracted: authors, place of the study and/or ethnicity, year of publication, sample size, study design, studied genes and SNPs, and outcome of the study.

5. Results

In this review during primary literature search, 219 and 1025 articles were identified through PubMed and HuGE Navigators databases, respectively (Figure 1).

After checking abstracts and titles, 49 articles from PubMed and 35 articles from HuGE Navigator databases were selected.

During 2 refining steps and after removing duplicates, 42 articles related to the study domain were selected. After quality assessment, 40 studies were selected for text appraisal, of which 38 qualified articles were evaluated at the final step (Figure 1). From finally included papers, 20 were conducted on healthy population (9-28), and 18 on obese children (29-46).

From reported studies, 19 (50%) had a cross- sectional design, 18 (47.36%) were case- control studies, and 1 (2.64%) was a prospective study. The age range of the studied population was 2 to 20 years. Table 1 displays the details of the 38 included studies.

According to the whole data of systematic review results, the number of total population and points of data was 14,536 (8,815 related to healthy population and 5,721 to obese children). Numbers of studied genes and related SNP were 60 (35 in healthy population and 25 in obese children) and 125 (69 in healthy population and 56 in obese children), respectively.

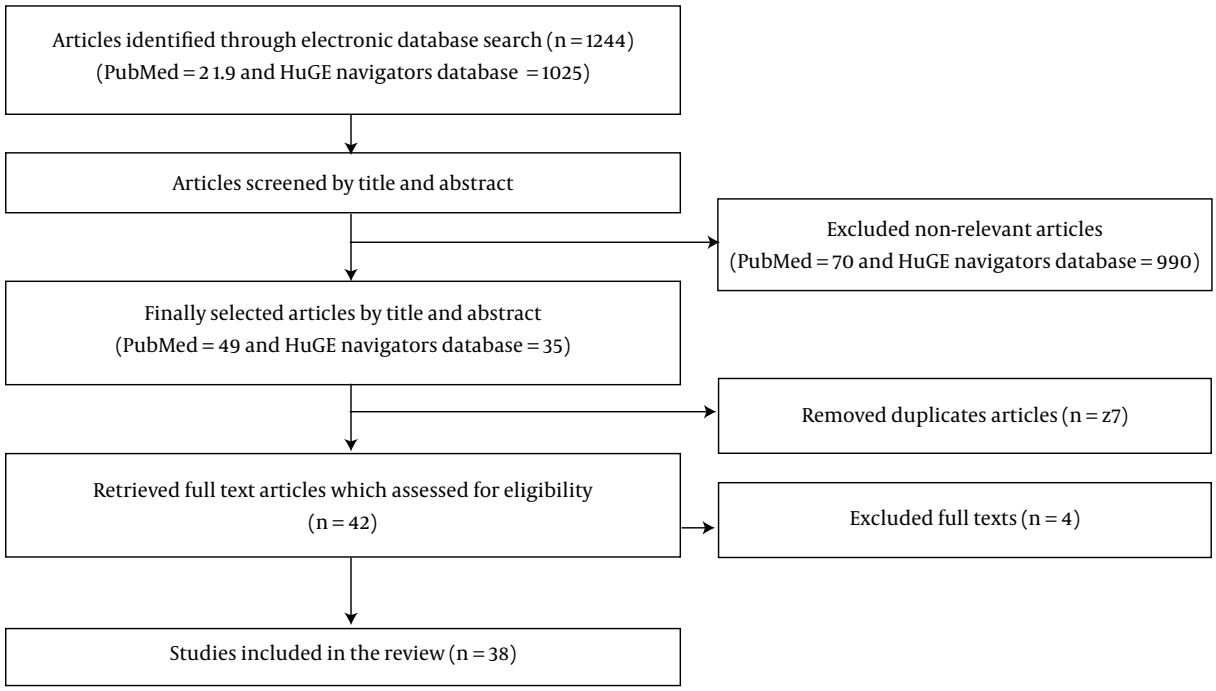

Figure 1. Flowchart of Study Selection

From studied SNPs in healthy population, 11 SNPs were associated with occurrence of MetS and 15 with different component of MetS. SNPs of the following genes were associated with MetS: GCK, HNFAα, SHBG, PON1, adiponectin, and obesity related genes (FTO, MC4R, GNPDA2, BDNF, FAIM2, NPC1, SEC16B, SH2B1, PCSK1, KCTD15, BAT2), PAI, AT1R, and SR-BI (9, 12-15, 20, 21, 26, 27).

SNPs of the following genes were associated with component of MetS: GCK, ACE, ABCA1, SREBP-1, miR-33b, PAI, IL6R, IL18, TCF7L2, ADRB2, and TNFα (9, 10, 17, 20, 22, 23, 25, 27, 28).

SNPs of the following genes did not have any association with MetS or its components: CRP, APOA5, PPARγ, PGC-1γ, and Tfam (11, 16, 18, 24).

From studied SNPs in obese children, 11 SNPs were associated with occurrence of MetS and 14 with different component of MetS. SNPs of the following genes were associated with MetS: PNPLA3, APO-A5, NPY, ADRB3, eNOS, and obesity related genes (TMEM18, SH2B1, KCTD15, PCSK1, BDNF, SEC16B, MC4R, and FTO), ENPP-1, PLIN, and INSVNTR (29, 31, 33-35, 37, 42, 44, 46).

SNPs of the following genes were associated with component of MetS: IL18, NPY, GHR, ACE, FABP4, ENPP-1, and PLIN (30, 33, 40).

SNPs of the following genes did not have any association with MetS or its components: IL6, IL6R, leptin-melanin, leptin, and TNFα (32, 36, 39, 43, 45).

6. Discussion

In this study, we reviewed all studies that evaluated the association between different SNPs of various genes with MetS among pediatric population. Our findings indicated that the frequency of the SNPs associated with different component of MetS were higher than those associated with Mets. In healthy population, most of the SNPs associated with MetS component are mainly related to the lipid metabolism, specially triglyceride and HDL (9, 16-18, 20, 22, 25), but in obese children most of SNPs were related to insulin resistance and lipid metabolism (30, 33, 40-42).

We did not find any review study in this field in literature review. Povel et al. have reported their findings from a systematic review and meta-analysis on adult population. They indicated that from 88 studies, which studied 25 genes, minor allele of FTO, TCF7L2, APOA5, APOC3, IL6 genes were more prevalent in MetS cases and a minor allele of CETP gene was less prevalent in participants with MetS. They concluded that lipid metabolism is considered as the most important component in the development of MetS (48).

In current review, most of the evaluated SNPs in healthy population were in association with lipids com-

ponent of MetS, and insulin resistance and lipid disorders were the main associated components in obese children. Some previous studies also indicated that the lipid genes and their metabolism pathway have a key role in the genetic background of MetS (49, 50). Kristiansson et al. conducted a genome-wide association (GWA) study to investigate the association between different identified susceptible loci for MetS with its component traits in 4 Finish cohort populations, with 2637 cases of MetS and 7927 control population. They indicated that susceptibility to MetS is commonly associated with genes and loci related to dyslipidemia and abdominal obesity. The most common related loci were lipid locus APOA1/C3/A4/A5 gene cluster region on Chromosome 11 (49).

In 2 studies, 1 conducted on healthy population and 1 on obese children, the association between obesity related SNPs with MetS was investigated (19, 37). The results of Zhao et al. study in China on healthy pediatric population revealed that from the studied 11 genes and their related 11SNPs, there were nominal associations between variants of GNPDA, BDNF, and FAIM2 gens with risk of MetS in children. They indicated that combination effect of studied SNPs was more significant in this field (19).

Dusatkova et al. in Czech Republic studied the association between 11 variants of 8 obesity related gens in obese children with MetS. They found that from the studied variants, rs925946 from BDNF gene and the 2 studied variants from MC4R gene were associated with MetS (37).

Considering the findings, it is suggested that combination effect of different obesity related SNPs would result in occurrence of MetS, or as mentioned by Aguilera et al. in Spain, the interaction between obesity related variants and environmental or lifestyle related factors results in development of MetS in children (5).

In the current review, 1 SNP has a protective effect for the occurrence of MetS in children. Alavi-shahri et al. in Iran demonstrated that the AT1R/A1166C polymorphism of AT1R gene have a protective effect on occurrence of MetS in adolescents (24).

Deram et al. in Brazil indicated that the PLIN6 14995A–> T was associated with better weight loss in obese children with MetS (44).

Another finding of our review was that some SNPs from specific genes did not have the same effect in obese and normal weight children.

Although some SNPs from inflammatory factors gens were associated with some component of MetS, none of them had any association with the development of MetS in children (11, 22, 23, 28, 30, 43, 45).

The implications of this review are that we can use the data of current review to design more epidemiological as well as interventional studies in the field of childhood Mets. Our data can be used for future epigenetic studies.

This review had some limitations. The number of studies included in this review was not large enough and there were not SNPs to perform meta-analysis.

The strength of this review was that no similar study has been conducted in this field on pediatrics population.

7. Conclusions

The findings of this review revealed that most reported SNPs related to MetS in children are associated with its components than with MetS. Most of the reported loci are related to lipid disorders, mainly triglyceride and HDL and insulin resistance. Furthermore, the polymorphisms were not similar in obese and non-obese children.

Combination effect of most of the reported SNPs or their interaction with environmental factors is more effective in developing MetS in children. Thus, it is highly recommended to conduct more studies to evaluate the interaction of different SNPs related to the components of MetS or interaction of SNPs-phenotype (such as obesity) in the occurrence of MetS.

Footnote

Conflict of Interest: Authors have no conflict of interest.

References

1. Alberti KG, Zimmet P, Shaw J, I. D. F. Epidemiology Task Force Consensus Group . The metabolic syndrome–a new worldwide definition. *Lancet.* 2005;**366**(9491):1059–62. doi: 10.1016/S0140-6736(05)67402-8. [PubMed: 16182882].
2. Weiss R. Childhood metabolic syndrome: must we define it to deal with it? *Diabetes Care.* 2011;**34 Suppl 2**:S171–6. doi: 10.2337/dc11-s214. [PubMed: 21525451].
3. Ford ES. The metabolic syndrome and mortality from cardiovascular disease and all-causes: findings from the National Health and Nutrition Examination Survey II Mortality Study. *Atherosclerosis.* 2004;**173**(2):309–14. doi: 10.1016/j.atherosclerosis.2003.12.022. [PubMed: 15064107].
4. Agirbasli M, Tanrikulu AM, Berenson GS. Metabolic Syndrome: Bridging the Gap from Childhood to Adulthood. *Cardiovasc Ther.* 2016;**34**(1):30–6. doi: 10.1111/1755-5922.12165. [PubMed: 26588351].
5. Aguilera CM, Olza J, Gil A. Genetic susceptibility to obesity and metabolic syndrome in childhood. *Nutr Hosp.* 2013;**28 Suppl 5**:44–55. doi: 10.3305/nh.2013.28.sup5.6917. [PubMed: 24010743].
6. Taylor JY, Kraja AT, de Las Fuentes L, Stanfill AG, Clark A, Cashion A. An overview of the genomics of metabolic syndrome. *J Nurs Scholarsh.* 2013;**45**(1):52–9. doi: 10.1111/j.1547-5069.2012.01484.x. [PubMed: 23368731].
7. Bellia A, Giardina E, Lauro D, Tesauro M, Di Fede G, Cusumano G, et al. "The Linosa Study": epidemiological and heritability data of the metabolic syndrome in a Caucasian genetic isolate. *Nutr Metab Cardiovasc Dis.* 2009;**19**(7):455–61. doi: 10.1016/j.numecd.2008.11.002. [PubMed: 19201175].

8. Wang XM. Early life programming and metabolic syndrome. *World J Pediatr.* 2013;**9**(1):5–8. doi: 10.1007/s12519-013-0403-7. [PubMed: 23389329].
9. Chang HW, Lin FH, Li PF, Huang CL, Chu NF, Su SC, et al. Association Between a Glucokinase Regulator Genetic Variant and Metabolic Syndrome in Taiwanese Adolescents. *Genet Test Mol Biomarkers.* 2016;**20**(3):137–42. doi: 10.1089/gtmb.2015.0241. [PubMed: 26799416].
10. Kim K, Ahn N, Park J, Koh J, Jung S, Kim S, et al. Association of angiotensin-converting enzyme I/D and alpha-actinin-3 R577X genotypes with metabolic syndrome risk factors in Korean children. *Obes Res Clin Pract.* 2016;**10 Suppl 1**:S125–32. doi: 10.1016/j.orcp.2015.09.008. [PubMed: 26483160].
11. Nikpour P, Emadi-Baygi M, Fatemi SG, Kelishadi R. Absence of association between -286C>A>T polymorphism in the CRP gene and metabolic syndrome in Iranian pediatric. *Adv Biomed Res.* 2015;**4**:210. doi: 10.4103/2277-9175.166147. [PubMed: 26605239].
12. Marcil V, Amre D, Seidman EG, Boudreau F, Gendron FP, Menard D, et al. Hepatocyte nuclear factor 4 alpha polymorphisms and the metabolic syndrome in French-Canadian youth. *PLoS One.* 2015;**10**(2):e0117238. doi: 10.1371/journal.pone.0117238. [PubMed: 25671620].
13. White MJ, Eren F, Agirbasli D, Williams SM, Agirbasli M. SHBG gene polymorphism (rs1799941) associates with metabolic syndrome in children and adolescents. *PLoS One.* 2015;**10**(2):e0116915. doi: 10.1371/journal.pone.0116915. [PubMed: 25647406].
14. Alegria-Torres JA, Garcia-Dominguez ML, Cruz M, Aradillas-Garcia C. Q192R polymorphism of paraoxonase 1 gene associated with insulin resistance in Mexican children. *Arch Med Res.* 2015;**46**(1):78–83. doi: 10.1016/j.arcmed.2014.12.001. [PubMed: 25500007].
15. Li P, Jiang R, Li L, Liu C, Yang F, Qiu Y. Correlation of serum adiponectin and adiponectin gene polymorphism with metabolic syndrome in Chinese adolescents. *Eur J Clin Nutr.* 2015;**69**(1):62–7. doi: 10.1038/ejcn.2014.152. [PubMed: 25074391].
16. Gamboa-Melendez MA, Galindo-Gomez C, Juarez-Martinez L, Gomez FE, Diaz-Diaz E, Avila-Arcos MA, et al. Novel association of the R230C variant of the ABCA1 gene with high triglyceride levels and low high-density lipoprotein cholesterol levels in Mexican school-age children with high prevalence of obesity. *Arch Med Res.* 2015;**46**(6):495–501. doi: 10.1016/j.arcmed.2015.07.008. [PubMed: 26256050].
17. Nikpour P, Miranzadeh-Mahabadi H, Emadi-Baygi M, Kelishadi R. Association of rs8066560 variant in the sterol regulatory element-binding protein 1 (SREBP-1) and miR-33b genes with hyperglycemia and insulin resistance. *J Pediatr Endocrinol Metab.* 2014;**27**(7-8):611–5. doi: 10.1515/jpem-2014-0115. [PubMed: 24825092].
18. Fatemi SG, Emadi-Baygi M, Nikpour P, Kelishadi R, Hashemipour M. Absence of Association between -1131T>C Polymorphism in the Apolipoprotein APOA5 Gene and Pediatric Metabolic Syndrome. *Iran J Pediatr.* 2014;**24**(3):319–22. [PubMed: 25562027].
19. Zhao X, Xi B, Shen Y, Wu L, Hou D, Cheng H, et al. An obesity genetic risk score is associated with metabolic syndrome in Chinese children. *Gene.* 2014;**535**(2):299–302. doi: 10.1016/j.gene.2013.11.006. [PubMed: 24269186].
20. De la Cruz-Mosso U, Munoz-Valle JF, Salgado-Goytia L, García-Carreón A, Illades-Aguiar B, Castaneda-Saucedo E, et al. Relationship of metabolic syndrome and its components with -844 G/A and HindIII C/G PAI-1 gene polymorphisms in Mexican children. *BMC Pediatr.* 2012;**12**(1) doi: 10.1186/1471-2431-12-41.
21. Juarez-Meavepena M, Carreon-Torres E, Lopez-Osorio C, Garcia-Sanchez C, Gamboa R, Torres-Tamayo M, et al. The Srb1+1050T allele is associated with metabolic syndrome in children but not with cholesteryl ester plasma concentrations of high-density lipoprotein subclasses. *Metab Syndr Relat Disord.* 2012;**10**(2):110–6. doi: 10.1089/met.2011.0071. [PubMed: 22182283].
22. Hsieh CH, Hung YJ, Wu LI, He CT, Lee CH, Hsiao FC, et al. Interleukin-6 receptor gene 48892 A/C polymorphism is associated with metabolic syndrome in female Taiwanese adolescents. *Genet Test Mol Biomarkers.* 2012;**16**(12):1376–81. doi: 10.1089/gtmb.2012.0188. [PubMed: 23094986].
23. Smart MC, Dedoussis G, Yiannakouris N, Grisoni ML, Dror GK, Yannakoulia M, et al. Genetic variation within IL18 is associated with insulin levels, insulin resistance and postprandial measures. *Nutr Metab Cardiovasc Dis.* 2011;**21**(7):476–84. doi: 10.1016/j.numecd.2009.12.004. [PubMed: 20227263].
24. Alavi-Shahri J, Behravan J, Hassany M, Tatari F, Kasaian J, Ganjali R, et al. Association between angiotensin II type 1 receptor gene polymorphism and metabolic syndrome in a young female Iranian population. *Arch Med Res.* 2010;**41**(5):343–9. doi: 10.1016/j.arcmed.2010.06.007. [PubMed: 20851291].
25. Liu PH, Chang YC, Jiang YD, Chen WJ, Chang TJ, Kuo SS, et al. Genetic variants of TCF7L2 are associated with insulin resistance and related metabolic phenotypes in Taiwanese adolescents and Caucasian young adults. *J Clin Endocrinol Metab.* 2009;**94**(9):3575–82. doi: 10.1210/jc.2009-0609. [PubMed: 19509102].
26. Gianotti TF, Sookoian S, Dieuzeide G, Garcia SI, Gemma C, Gonzalez CD, et al. A decreased mitochondrial DNA content is related to insulin resistance in adolescents. *Obesity (Silver Spring).* 2008;**16**(7):1591–5. doi: 10.1038/oby.2008.253. [PubMed: 18451773].
27. Park HS, Shin ES, Lee JE. Genotypes and haplotypes of beta2-adrenergic receptor and parameters of the metabolic syndrome in Korean adolescents. *Metabolism.* 2008;**57**(8):1064–70. doi: 10.1016/j.metabol.2008.03.009. [PubMed: 18640383].
28. Sookoian S, Garcia SI, Gianotti TF, Dieuzeide G, Gonzalez CD, Pirola CJ. The G-308A promoter variant of the tumor necrosis factor-alpha gene is associated with hypertension in adolescents harboring the metabolic syndrome. *Am J Hypertens.* 2005;**18**(10):1271–5. doi: 10.1016/j.amjhyper.2005.04.014. [PubMed: 16202847].
29. Mangge H, Baumgartner BG, Zelzer S, Pruller F, Schnedl WJ, Reininghaus EZ, et al. Patatin-like phospholipase 3 (rs738409) gene polymorphism is associated with increased liver enzymes in obese adolescents and metabolic syndrome in all ages. *Aliment Pharmacol Ther.* 2015;**42**(1):99–105. doi: 10.1111/apt.13232. [PubMed: 25939720].
30. Suazo J, Smalley SV, Hodgson MI, Weisstaub G, Gonzalez A, Santos JL. [Association between genetic polymorphisms of interleukin 6 (IL6), IL6R and IL18 with metabolic syndrome in obese Chilean children]. *Rev Med Chil.* 2014;**142**(3):290–8. doi: 10.4067/S0034-98872014000300002. [PubMed: 25052265].
31. Zaki M, Amr K. Apolipoprotein A5 T-1131C variant and risk for metabolic syndrome in obese adolescents. *Gene.* 2014;**534**(1):44–7. doi: 10.1016/j.gene.2013.10.032. [PubMed: 24161374].
32. Suazo J, Hodgson MI, Obregon AM, Valladares M, Weisstaub G, Amador P, et al. Prevalence of metabolic syndrome in obese Chilean children and association with gene variants of the leptin-melanocortin system. *J Pediatr Endocrinol Metab.* 2013;**26**(11-12):1131–9. doi: 10.1515/jpem-2013-0084. [PubMed: 23817596].
33. Olza J, Gil-Campos M, Leis R, Ruperez AI, Tojo R, Canete R, et al. Influence of variants in the NPY gene on obesity and metabolic syndrome features in Spanish children. *Peptides.* 2013;**45**:22–7. doi: 10.1016/j.peptides.2013.04.007. [PubMed: 23624317].
34. Oguri K, Tachi T, Matsuoka T. Visceral fat accumulation and metabolic syndrome in children: the impact of Trp64Arg polymorphism of the beta3-adrenergic receptor gene. *Acta Paediatr.* 2013;**102**(6):613–9. doi: 10.1111/apa.12149. [PubMed: 23282015].
35. Miranda JA, Belo VA, Souza-Costa DC, Lanna CM, Tanus-Santos JE. eNOS polymorphism associated with metabolic syndrome in children and adolescents. *Mol Cell Biochem.* 2013;**372**(1-2):155–60. doi: 10.1007/s11010-012-1456-y. [PubMed: 22983816].
36. Komsu-Ornek Z, Demirel F, Dursun A, Ermis B, Piskin E, Bideci A. Leptin receptor gene Gln223Arg polymorphism is not associated with obesity and metabolic syndrome in Turkish children. *Turk J Pediatr.* 2012;**54**(1):20–4. [PubMed: 22397037].
37. Dusatkova L, Zamrazilova H, Sedlackova B, Vcelak J, Hlavaty P, Aldhoon Hainerova I, et al. Association of obesity susceptibility gene variants

with metabolic syndrome and related traits in 1,443 Czech adolescents. *Folia Biol (Praha).* 2013;**59**(3):123–33. [PubMed: 23890480].
38. Gao L, Zheng Z, Cao L, Shen S, Yang Y, Zhao Z, et al. The growth hormone receptor (GHR) exon 3 polymorphism and its correlation with metabolic profiles in obese Chinese children. *Pediatr Diabetes.* 2011;**12**(4 Pt 2):429–34. doi: 10.1111/j.1399-5448.2010.00747.x. [PubMed: 21470351].
39. Pyrzak B, Wisniewska A, Popko K, Demkow U, Kucharska AM. Association between anthropometric measures of obesity, metabolic disturbances and polymorphism G-308A of the tumor necrosis factor-alpha gene in children. *Eur J Med Res.* 2010;**15 Suppl 2**:141–6. [PubMed: 21147642].
40. Shcherbakova M, Sinitsin PA, Poriadina GI, Larionova VI, Khmyrova AP, Petriaĭkina EE, et al. Correlation of metabolic syndrome clinical signs and genetic determinants at children with obese. *Eksperimental'naia i klinicheskaia gastroenterologiia.* 2009(7):6–11.
41. Khalyfa A, Bhushan B, Hegazi M, Kim J, Kheirandish-Gozal L, Bhattacharjee R, et al. Fatty-acid binding protein 4 gene variants and childhood obesity: potential implications for insulin sensitivity and CRP levels. *Lipids Health Dis.* 2010;**9**:18. doi: 10.1186/1476-511X-9-18. [PubMed: 20156355].
42. Santoro N, Cirillo G, Lepore MG, Palma A, Amato A, Savarese P, et al. Effect of the rs997509 polymorphism on the association between ectonucleotide pyrophosphatase phosphodiesterase 1 and metabolic syndrome and impaired glucose tolerance in childhood obesity. *J Clin Endocrinol Metab.* 2009;**94**(1):300–5. doi: 10.1210/jc.2008-1659. [PubMed: 18940878].
43. Pyrzak B, Wisniewska A, Majcher A, Popko K, Wasik M, Demkow U. Association between metabolic disturbances and G-174C polymorphism of interleukin-6 gene in obese children. *Eur J Med Res.* 2009;**14 Suppl 4**:196–200. [PubMed: 20156756].
44. Deram S, Nicolau CY, Perez-Martinez P, Guazzelli I, Halpern A, Wajchenberg BL, et al. Effects of perilipin (PLIN) gene variation on metabolic syndrome risk and weight loss in obese children and adolescents. *J Clin Endocrinol Metab.* 2008;**93**(12):4933–40. doi: 10.1210/jc.2008-0947. [PubMed: 18812483].
45. Pyrzak B, Wiśniewska A, Rymkiewicz-Kluczynska B. Tumor necrosis factor alpha (TNF-alpha) gene G-308A polymorphism relationship to insulin resistance and lipid abnormalities in children with obesity. *Endokrynologia, diabetologia i choroby przemiany materii wieku rozwojowego: organ Polskiego Towarzystwa Endokrynologow Dzieciecych.* 2005;**12**(3):171–4.
46. Santoro N, Cirillo G, Amato A, Luongo C, Raimondo P, D'Aniello A, et al. Insulin gene variable number of tandem repeats (INS VNTR) genotype and metabolic syndrome in childhood obesity. *J Clin Endocrinol Metab.* 2006;**91**(11):4641–4. doi: 10.1210/jc.2005-2705. [PubMed: 16868061].
47. Palomaki GE, Melillo S, Bradley LA. Association between 9p21 genomic markers and heart disease: a meta-analysis. *JAMA.* 2010;**303**(7):648–56. doi: 10.1001/jama.2010.118. [PubMed: 20159873].
48. Povel CM, Boer JM, Reiling E, Feskens EJ. Genetic variants and the metabolic syndrome: a systematic review. *Obes Rev.* 2011;**12**(11):952–67. doi: 10.1111/j.1467-789X.2011.00907.x. [PubMed: 21749608].
49. Kristiansson K, Perola M, Tikkanen E, Kettunen J, Surakka I, Havulinna AS, et al. Genome-wide screen for metabolic syndrome susceptibility Loci reveals strong lipid gene contribution but no evidence for common genetic basis for clustering of metabolic syndrome traits. *Circ Cardiovasc Genet.* 2012;**5**(2):242–9. doi: 10.1161/CIRCGENETICS.111.961482. [PubMed: 22399527].
50. Stancakova A, Laakso M. Genetics of metabolic syndrome. *Rev Endocr Metab Disord.* 2014;**15**(4):243–52. doi: 10.1007/s11154-014-9293-9. [PubMed: 25124343].

Table 1. Details of Studied Evaluated the Association of Different Single-Nucleotide Polymorphisms(SNPs) with Development of Metabolic Syndrome in Children and Adolescents

			Population	Gene	Polymorphism	Outcome
1	Chang et al. (9) 2016 (Taiwan)	The association between Glucokinase Regulator Genetic Variant and Metabolic Syndrome among Taiwanese adolescents was investigated.	962 adolescents (468male and 494 female)	Glucokinase Regulator	rs780094	The rs780094 variants of GCKR gene were significantly associated with Met s and level of HDL-C.
2	Kim et al. (10) 2015 (Korea)	The interaction of angiotensin-converting enzyme I/D and α-actinin-3 R577X in the occurrence of MetS.	788 elementary school children (mean age 10.10 $\pm$ 0.07 y).	ACTN3 and ACE gene	ACE I/D or the ACTN3 R577X polymorphisms	The children having both ACE I/D or the ACTN3 R577X polymorphisms and ACE DD genotype had high systolic blood pressure and low blood HDL cholesterol level.
3	Nikpour et al. (11) 2015 (Iran)	The association between rs3091244 variant of the C-reactive protein (CRP) gene and MetS in Iranian children and adolescents was determined	100 children with MetS and 100 normal children aged 9-19 years	CRP	rs3091244 variant	The polymorphism is not associated with increased risk of MetS among Iranian children and adolescents
4	Mangge et al. (29) 2015 (Austria)	The effect of patatin-like phospholipase 3 (PNPLA3) rs738409 (Ile148Met, C > G) gene polymorphism on overweight/obese adolescents with and without metabolic syndrome (MetS) was evaluated.	288 overweight/obese and 209 normal weight participants of the STYJOBS/EDECTA cohort were analyzed for PNPLA3 genotypes	Patatin-like phospholipase 3 (PNPLA3)	rs738409 (Ile148Met, C > G) gene	MetS & O Presence of the G allele (148Met) was significantly higher in overweight/obese adolescents with MetS than those without. adolescents with homozygote G allele had increased level of ALT.They recommended that overweight/obese adolescents with rs738409 polymorphism should be educated for lifestyle modification
5	Marcil et al. (12) 2015 (Canada)	The relationship between HNF4A genetic variants of Hepatocyte nuclear factor 4 alpha (HNF4α) gene with MetS and its components was investigated.	1,749 French-Canadians aged 9, 13 and 16 years evaluated for HNF4α gene polymorphism	Hepatocyte nuclear factor 4 alpha (HNF4α) gene	rs6130608-rs2425637; rs736824; rs736824 - rs745975 - rs3212183	There was significant association between HNF4α genetic variants and MetS among pediatrics population. According to their suggestion HNF4α could be used as an early marker for the risk of developing of type 2 diabetes mellitus.
6	White et al. (13) 2015 (Turkey)	The association between sex hormone binding globulin (SHBG) gene polymorphism (rs1799941) with metabolic syndrome in children and adolescents	360 schoolchildren with MetS from Turkish pediatric cohort (37 cases, 323 controls)	sex hormone binding globulin (SHBG)	rs1799941	There was significant association between rs1799941, located in SHBG, and MetS

7	Alegria-Torres (14) et al. 2015 (Mexico)	During this study, DNA samples of studied children were genotyped for Q192R polymorphism of the PON1 gene.	117 children aged 6 - 12 years	paraoxonase 1 gene (PON1)	rs662	They indicated that PON1 Q192R polymorphism considered as a risk factor for the development of metabolic syndrome in children.
8	Li et al. (15) 2015 (China)	The association between polymorphisms of adiponectin gene and MetS and cardiovascular disease risk factors was investigated	919 healthy middle school students aged 11 - 16 years studied in a cross sectional study.	Adiponectin gene	(SNPs) rs266729 (-11377C/G), rs2241766 (+45T/G) and rs1501299 (+276G/T)	There was significant association between the polymorphisms of Adiponectin gene and MetS.
9	Gamboa-Melendez et al. (16) 2015 (Mexico)	The role of R230C variant of the ABCA1 gene in occurrence of MetS and other metabolic traits was evaluated.	432 schoolchildren aged 6 - 13 y	ABCA1 gene	R230C	The R230C variant of the ABCA1 gene was not associated with MetS but with some of its components including HDL-cholesterol and triglyceride
10	Suazo et al. (30) 2014 (Chile)	The association between different varients of L6, IL6R and IL18 genes and occurrence of MetS and its components was evaluated.	259 obese children(BMI > 26 $\pm$ 4.1 kg/m^2) aged 8 - 12 y	L6, IL6R and IL18	of IL6 (rs1800795, rs1800796 and rs1800797), IL6R (rs2228145) and IL18 (rs360719, rs187238 and rs204355)	There was not any significant association between IL^ and IL6R gene polymorphisms and MetS and its components. There was significant correlation between IL18 haplotypes and components of MetS including triglycerides and HDL.
11	Nikpour et al. (17) 2014 (Iran)	The association between rs8066560 variant in the sterol regulatory element-binding protein 1 (SREBP-1) and miR-33b genes with insulin resistance	200 participants aged 9 - 19 y (100 with MetS and 100 healthy controls)	SREBP-1 and miR-33b genes	rs8066560	There was not any significant association between rs8066560 polymorphism and MetS, hyperglycemia, and insulin resistance in studied population. They found a significant association between rs8066560 polymorphism and LDL-C levels in adolescents.
12	Fatemi et al. (18) 2014 (Iran)		100 children and adoelsenctes in a case control study comprised 50 cases of MetS and 50 controls	Apolipoprotein APOA5 Gene	-1131T > C polymorphism.	There was not any association between -131T > C polymorphism of the APOA5 gene and triglyceride levels and MetS in children and adolescents.
13	Zhao et al. (19) 2014 (China)	The association between obesity related polymorphisms with MetS in children was investigated.	431 children with MetS and 3046 controls	FTO, MC4R, GNPDA2, BDNF, FAIM2, NPC1, SEC16B, SH2B1, PCSK1, KCTD15, BAT2	rs9939609 (FTO), rs17782313 (MC4R), rs10938397 (GNPDA2), rs6265(BDNF), FAIM2 rs7138803, rs1805081(NPC1), rs10913469 (SEC16B), rs4788102(SH2B1), rs6235 (PCSK1), rs29941 (KCTD15), s2844479 (BAT2)	They demonstrated a nominal associations between variants of GNPDA, BDNF and FAIM2 with risk of MetS in children. They indicated that combination effect of studied SNPs were more significant in this field.

14	Zaki et al. (31) 2014 (Egypt)	The association between a variant of Apolipoprotein A5 gene with development of MetS among obese adolescents was investigated.	150 obese adolescents with MetS and 204 healthy normal weight adolescents aged 17 -2 0 years old	Apolipoprotein A5	T-1131C	Presence of the studied polymorphism of Apolipoprotein A5 gene is considered as a risk factor for occurrence of MetS in obese adolescents.
15	Suazo et al. (32) 2013 (Chile)	The association between common genetic variants of leptin-melanocortin pathway genes including LEP, LEPR, POMC, MC3R and MC4R with components of the MS in obese children was investigated.	259 obese children aged 6 - 12 y	(LEP, LEPR, POMC, MC3R and MC4R)	-	There was not any association between genetic variants of leptin-melanocortin genes and MS components.
16	Olza et al. (33) 2013 (Spain)	The association between four SNPs of Neuropeptide Y (NPY) gene with different components of MetS, anthropometric measurements, adipokines, inflammatory and CVD risk biomarkers and clinical and other metabolic markers was investigated.	In a case-control study, 292 obese children and 242 normal weight children aged 5 - 15 y	Neuropeptide Y (NPY) gene	rs16131, rs16178 or rs16135, rs16147.	The association between rs16147 with insulin resistance, triacylglycerols, leptin, and HDL-c was confirmed. The association between rs16131 with obesity early onset of MetS and its component specially triacylglycerols was determined for the first time.
17	Oguri et al. (34) 2013 (Japan)	The impact of three polymorphisms of the beta3-adrenergic receptor gene with Visceral fat accumulation and metabolic syndrome in children was investigated.	132 children aged 6 - 12 y (73 obese and 59 non obese)	Beta3-adrenergic receptor (ADRB3) gene	Trp64Arg; Trp64Trp; Arg64Arg	There was significant association between Trp64Arg polymorphism of ADRB3 gene and visceral fat accumulation and MetS in Japanese children
18	Miranda et al. (35) 2013 (Brazil	The distribution of eNOS gene polymorphism was compared in three groups of children and adolescents (normal, obese and those with Mets)	242 children in three control (108), obese (64) and MetS (70) groups	Endothelial nitric oxide (eNOS)	rs 2070744, 27-bprepeat, rs 1799983	In obese children and adolescents there was a significant association between the CC genotype for the T (786)C polymorphism of eNOS gene and MetS.
19	De la Cruz-Mosso et al. (20) 2012 (Mexico)	The association between two SNPs of Plasminogen activator inhibitor-1 gene with MetS was determined.	100 children aged 6-11 years in two groups of with and without MetS	Plasminogen activator inhibitor-1 (PAI-1)	-844 G/A PAI-1 , HindIII C/G PAI-1	There was significant association between -844 G/A PAI-1 and obesity, dyslipidemia and development of Mets in children. There was significant association between HindIII C/G PAI-1 and high level of cholesterol in Mexican children.
20	Komşu-Ornek et al. (36) 2012 (Turkey)	The association between Gln223Arg polymorphism of Leptin receptor gene and serum insulin and lipid levels in two group of obese and non obese children was investigated.	92 obese (23with MetS) and 99 lean children aged 5 - 15 y	Leptin receptor gene	Gln223Arg	There was not any significant association between Gln223Arg polymorphism and serum insulin and lipid levels in studied groups of children.

21	Juarez-Meavepena et al. (21) 2012 (Mexico)	The association between a polymorphism of scavenger receptor class B type I gene with Mets and HDL was evaluated.	39 children and adolescents with MetS and 65 controls aged 6 - 17 y	scavenger receptor class B type I (SR-BI) [HDL]	The Srb1 + 1050C- > T (rs5888) single-nucleotide polymorphisms	Association between the studied polymorphism and MetS was determined but in T carriers there was not any association with HDL.
22	Hsieh et al. (23) 2012 (Taiwan)	Frequencies and impact of the IL-6R 48892 polymorphism in MetS of adolescents were evaluated	925 adolescents (451 boys and 474 girls)	IL6 receptor gene	48892 A/C	The 48892 A/C polymorphism of IL6 receptor gene was associated with high triglyceride (significantly in boys) and waist circumference and low HDL-C levels (significantly in girls) in adolescents. The association had different features in boys and girls.
23	Dusatkova et al. (37) 2013 (Czech Republic)	Association of some obesity susceptibility gene variants with MetS was evaluated.	1,443 adolescents aged 13.0-17.9 years in two groups of undwerweight/normal weight and overweight/obese	TMEM18, SH2B1, KCTD15, PCSK1, BDNF, SEC16B, MC4R, and FTO	rs7561317 (TMEM18), rs7498665 (SH2B1), rs29941 (KCTD15), rs6232 and rs6235 (PCSK1), rs925946 and rs4923461 (BDNF), rs10913469 (SEC16B), rs12970134 and rs17782313 (MC4R), rs9939609 (FTO)	From studied variants, rs925946 from BDNF gene and the two studied variants from MC4R gene were associated with MetS.
24	Gao et al. (38) 2011 (China)	The association between d3-GHR polymorphism of growth hormone receptor gene with metabolic parameters and BMI of obese children was investigated.	409 overweight/obese and 206 normal weight children	Growth hormone receptor gene	d3-GHR	The studied poly morphism had protective effect on BMI,insulin resistance and serujm cholesterol level of obese/overweight children
25	Smart et al. (23) 2011 (Greece)	The association between five polymorphisms of IL 18 gene with insulin levels, insulin resistance and postprandial measures was evaluated.	882 children and adolescents from the Gene e Diet Attica Investigation on childhood obesity (GENDAI) study	IL18 gene	rs1946519, rs2043055, rs549908, rs360729, rs3882891	There was only modest association between rs2043055 and systolic and diastolic blood pressure.
26	Pyrzak et al. (39) 2010 (Poland)	To evaluate the possible impact of G-308A polymorphism of the TNF-α gene with grade of obesity, insulin resistance, lipid profile, leptin levels, and the incidence of metabolic syndrome in obese children.	124 obese children and adolescents aged 10 - 18 years old	TNF-α gene	G-308A polymorphism	Though the frequency of the polymorphism is significantly higher in obese children but it had not significant association with the grade of obesity, insulin resistance, lipid profile, leptin levels, and the incidence of metabolic syndrome in obese children.
27	Shcherbakova et al. (40) 2010 (Russia)	The association between polymorphisms of ACE gene and components of metabolic syndrome was evaluated.	148 obese and 46 normal weight children	ACE gene	G-75A ApoA1, S19W ApoA5, SstI ApoC3, E2/E3/E4 ApoE and W/R ADRB3.	There was significant association between studied polymorphism of ACE gene and high blood pressure, serum lipids, hyperglycemia and hyperinsulinemia.

28	Alavi-Shahri et al. (24) 2010 (Iran)	The association between Angiotensin II type I receptor gene polymorphism and MetS among female adolescents was investigated.	350 adolescent girls aged 15 - 17 years with (101) and without (249) MetS	Angiotensin II type I receptor (AT1R)	AT1R/A1166C	The AT1R/A1166C polymorphism of AT1R gene have protective effect on occurrence of MetS in Adolescents.
29	Khalyfa et al. (41) 2010 (USA)	The association between 4 allelic variants of Fatty-acid binding protein 4 (FABP4) gene with insulin sensitivity of children was investigated.	309 children ages 5 - 7 years with (182) and without (127) obesity	Fatty-acid binding protein 4	rs1051231, rs2303519, rs16909233 and rs1054135	From studied allelic variants, rs16909233 variant allele was associated with insulin resistance in both obese and non obese children.
30	Santoro et al. (42) 2009 (Italy)	The association between rs997509 polymorphism of nucleotide pyrophosphatase/phospl 1 (ENPP-1) gene with MetS and and impaired glucose tolerance of children was determined.	809 children aged 2-16 years in two obese (409) and non obese (400) groups	nucleotide pyrophosphatase/phospl 1 (ENPP-1) gene	K121Q and rs997509 ENPP-1 variants	The polymorphism could predict occurrence of MetS and IGF in obese children .In addition it was significant association between the polymorphism and insulin resistance.
31	Pyrzak et al. (43) 2009 (Poland)	The association between G-174C polymorphism of interleukin-6 gene with component of MetS among obese children was investigated.	124 obese and 56 non-obese children	interleukin-6 gene	174G > C	There was not any association between the G-174C polymorphism of interleukin-6 gene and obesity and MetS in children
32	Daram et al. (44) 2008 (Brazil)	The impact of four perilipin (PLIN) gene variants on Mets and weight loss of obese children and adolescents was evaluated.	234 obese children and adolescents aged 7 - 14 y	Perilipin (PLIN)	PLIN1 6209T–> C, PLIN4 11482G–> A, PLIN5 13041A–> G, PLIN6 14995A–> T	The PLIN4 11482G–> A was associated with the risk of Mets. The PLIN6 14995A–> T was associated with better weight loss.They concluded that the gene could predict outcome according to the treatment options used for this group of population.
33	Liu et al. (25) 2009 (Taiwan)	The impact of nineteen single nucleotide polymorphisms (SNPs) of TCF7L2 gene on insulin resistance and related features of MetS was investigated.	525 Taiwanese adolescent twin-pairs and siblings.	TCF7L2	rs6585194, rs7919409, rs11196219, rs4918792, rs10749127, rs11196224, rs7085532, rs17130188, rs10787475, rs12775879, rs290498, rs290487, rs290481, (rs7079711, rs4506565, rs7903146, rs12243326, rs7895340, rs12255372	From 19 SNPs, two of them rs290487 and rs10749127 C were associated with insulin resistance and some features of MetS including blood pressure and triglyceride, respectively.
34	Gianotti et al. (26) 2008 (Argentina)	In order to determine the relation between a decreased mitochondrial DNA content and insulin resistance in adolescents ,the impact of peroxisome proliferator-activated receptor-gamma, PPAR- gamma coactivator-1alpha and Tfam genes polymorphisms on the development of insulin resistance in adolescents was investigated.	175 high school students	peroxisome proliferator-activated receptor-gamma (PPAR-γ), PPAR-gamma coactivator-1alpha (PGC-1α) and Tfam	pro12Ala (PPAR-γ), Gly482Ser (PGC-1α), rs1937 and rs12247015 (Tfam)	There was not any difference in the frequency of mentioned variants in adolescents with and without insulin resistance

35	Park et al. (27) 2008 (Korea)	The association between five polymorphisms of beta (2)-adrenergic receptor (ADRB2) gene with parameters of the metabolic syndrome among adolescents was investigated.	134 adolescents (69 male and 65 female).	beta(2)-adrenergic receptor (ADRB2) gene	rs1042713 , rs1042714 , rs1042717, rs1042718 , rs1042719	The rs1042714 SNP was associated with higher body fat, waist circumference, and free fatty acids. The rs1042717 SNP was associated with higher body weight, fasting insulin, and HOMA score. The rs1042714, rs1042717, rs1042718, and rs1042719 was associated with higher body weight, fasting insulin, and HOMA score.
36	Santoro et al. (46) 2006 (Italy)	The association between variants of Insulin gene promoter (INS VNTR) and MetS was evaluated.	320 obese children	Insulin gene promoter (INS VNTR)		The I variant of INS VNTR gene could predispose obest children to develop MetS.
37	Pyrzak et al. (45) 2005 (Poland)	The association between G-308A polymorphism of Tumor necrosis factor (TNF-α) gene with insulin resistance	72 obese children and adolescents aged 9 - 18 y	Tumor necrosis factor (TNF-α) gene	G-308A	There was not any association between studied varients of TNF-α gene and insulin resistance as well as degree of obesity
38	Sookoian et al. (28) 2005 (Argantina)	The association between the G-308A variant of TNF-alpha gene and different component of MetS among adolescents harboring the MetS was investigated	175 adolescents with high systoloic or diastolic blood pressure	Tumor necrosis factor-alpha	G-308A	There was significant association between the G-308A variant of TNF-alpha gene and systolic arterial BP and HOMA index in adolescents harboring the MetS.