# GENETICS AND ETIOPATHOLOGY OF CHILDHOOD OBESITY, AND DEVELOPMENT OF A GENETIC RISK CALCULATION PANEL BASED ON THE POLYGENIC RISK SCORE APPROACH

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# ABSTRACT


## GENETICS AND ETIOPATHOLOGY OF CHILDHOOD OBESITY, AND DEVELOPMENT OF A GENETIC RISK CALCULATION PANEL BASED ON THE POLYGENIC RISK SCORE APPROACH

Obesity is the disease that significantly affects human life as a combination of genetic and physiological environment. The polygenic background of the disease causes of childhood or adulthood obesity are still not fully understood. Childhood obesity and adulthood obesity are usually expressed in terms of body fat mass and body mass index (BMI). Obesity is a comorbid disease that is often associated with T2D, cardiovascular diseases, fatty liver and various mental health problems. Therefore, examining the genetic background of the disease is also important for epidemiological studies.

Obesity, which is one of the multi-gene diseases, is revealed by genome-wide research studies, candidate gene studies by SNP genotyping assays. SNP genotyping analyzes not only provide information about the transmission of childhood obesity, but also provide significant guidance on the biological pathways of the disease.

Genome-wide association studies (GWAS) provide effective research in association studies between anthropometric body characteristics and the genome.

The aim of this thesis is to investigate childhood related obesity variants, adulthood related obesity variants, to identify relationship of these two groups of genetic variants. In addition, the purpose of the thesis, is to understand effects of the variants on metabolic pathways, the difference of childhood and adulthood obesity related pathways and calculation of polygenic risk .

# ÖZET

## ÇOCUKLUK ÇAĞI OBEZİTESİNİN GENETİĞİ VE ETİYOPATOLOJİSİ VE POLİGENİK RİSK PUANI YAKLAŞIMINA DAYALI GENETİK RİSK HESAPLAMA PANELİNİN GELİŞTİRİLMESİ

Obezite, genetik ve fizyolojik çevrenin bileşkesi olarak insan yaşamını önemli ölçüde etkileyen bir hastalıktır. Çocukluk ya da erişkinlik obezitesine neden olan hastalığın poligenik geçmişi hala tam olarak anlaşılamamıştır. Çocukluk çağı obezitesi ve yetişkinlik obezitesi genellikle vücut yağ kütlesi ve vücut kitle indeksi (VKİ) cinsinden ifade edilir. Obezite, genellikle tip 2 diyabet, kardiyovasküler hastalıklar, karaciğer yağlanması ve çeşitli zihinsel sağlık sorunları ile ilişkilendirilen komorbid bir hastalıktır. Bu nedenle hastalığın genetik altyapısının incelenmesi epidemiyolojik çalışmalar için de önemlidir.

Çoklu gen hastalıklarından biri olan obezite, genom çapında araştırma çalışmaları, aday gen çalışmaları, SNP genotipleme testleri ile ortaya çıkarılmaktadır. SNP genotipleme analizleri sadece çocukluk çağı obezitesinin aktarımı hakkında bilgi sağlamakla kalmaz, aynı zamanda hastalığın biyolojik yolları hakkında da önemli rehberlik sağlar.

Genom çapında ilişkilendirme çalışmaları (GWAS), antropometrik vücut özellikleri ile genom arasındaki ilişkilendirme çalışmalarında etkili araştırmalar sağlar.

Bu tezin amacı, çocukluk çağına bağlı obezite varyantlarını, yetişkinliğe bağlı obezite varyantlarını araştırmak ve bu iki genetik varyant grubu arasındaki ilişkiyi belirlemektir. Ayrıca varyantların metabolik yolaklar üzerindeki etkilerini, çocukluk ve erişkinlik obezite ilişkili yolaklar arasındaki farkı ve poligenik risk skorunun hesaplanmasını anlamak da tezin amacını oluşturmaktadır.

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# CHAPTER 1

# INTRODUCTION

## 1.1 Pathophysiology of Obesity

### 1.1.1 Obesity

Obesity or being overweight is, by definition, the intake of more energy than the body needs, and accordingly, the formation of a high rate of fat tissue in the body. There are lots of cause of being obese; lifestyle, genetic factors and also environmental conditions. Obesity is a complex disease that has attracted attention especially in the last century. Obesity can be morbid that has more than one high risk in certain conditions. It may be seen with other highly risky conditions such as Type 2 Diabetes, cardiovascular diseases, cancer, and developmental disorders in children (Loos, R.J.F. et al. 2022; Chung, W. K. 2012).

Due to two different major reasons, genetic and environmental, obesity as a severe disease may restrict the wellness of individuals and even results in death. Environmental conditions, of course, include conditions such as access to healthy food, sleeping cycles, regular and healthy working and living conditions, daily eating habits, regular movement, and sports (Khanna, D. 2022; Mahmoud, A. 2022).

Obesity threatens global public health in both developed and undeveloped countries. According to recent studies, Nauru has an obesity rate at 61% and Palau follows with 55.3% obesity rate in 2023. Middle East countries such Kuwait, Saudi Arabia, Qatar, Jordan have around 35% obesity rate and ranked in most obese countries worldwide (Brittanica ProCon, 2020). Turkey is one of the risky developing countries in both Europe and worldwide. According to Turkish Statistical Institute (TUIK), in 2019, obesity rate over 15 years

increased from 19,6% to 21,1%. When compared the sex difference, the results indicated that women became 24,8% obese and 30,4% overweight and, men became 39,7% overweight and 17,3% obese (TUIK, 2020).

Childhood and adulthood obesity prevalence increasing every year. From 1975 to 2010, the obese people rate tripled in the worldwide. Obesity become one of the most threatening noninfectious disease due to comorbidity and mortality risks (Loos, R.J.F. et al. 2022; ProCon, 2020).

## 1.2 Environmental Factors

### 1.2.1 Eating Habits

Obesity primarily intake of excess energy and consuming less calories in daily dietary basis. Eating is a complex behavior consisting of many sub-titles such as socio-economic status, culture, economy, access to healthy food, and education (Xie, Qi.2019).

Economy and socio-economic status, the difficulty of accessing healthy food, especially in developing countries, and the tendency of the group which is in the lower economic classes in developed countries to fast consumption, high-calorie, low-cost foods increase the risk of obesity in this century. Most of the working population also consumes to easy accessible, fast food type packaged and processed foods (Anekwe, C. V. 2020).

Especially in the last hundred years, the risk of being obese increases for individuals who are fed with packaged and processed foods that contains added sugar, high saturated fat and lower fiber content. The trouble of preparing healthy natural foods, working and educational conditions leading to fast consumption food products, food crises in developing countries also increase such consumption habits (Harvard T.H Chan School of Public Health Obesity Prevention Source, 2023; Xie, Qi.2019).

Eating habits does not only affected by daily habits but also energy taking pathways that is regulated by Leptin- Melanocortin pathways. Leptin Melanocortin pathways are first described in mouse models with mutations in specific genes that plays role in the pathway. Because this pathway regulates the appetite and energy intake in the body, mutations in the

genes directly affects the body composition. Mutations in the pathway is described monogenic non-syndromic obesity and the risk of disease was better understood with mouse models (Mancuso, C. 2019; Mahmoud, A. 2022).

### 1.2.2 Sleep Duration and Obesity risk

Sleep patterns are associated with eating habits, Type 2 Diabetes and obesity (Zhou, Q. 2023). In the modern world, sleeping habits have changed considerably with working conditions. The inefficiency of night sleep, night work and shifts, irregularity of sleep and mealtimes reveal the health problems. The association of biological activities with sleep, called the circadian clock, is effective in almost all tissues in the body. Circadian clock is directly effective in the balanced functioning of hormones in the body between daylight and nightfall (Mahmoud, A. 2022). Researches and evidences suggested that, night shifts and sleep durations less than 8 hour have %15 effect on adult and young women obesity risk and Type 2 Diabetes. Additionally, study with children and adolescents with different sleep duration showed that, obesity, being overweight and larger waist circumference is related with shorter sleep duration. This is because, genes that play crucial role in circadian clock directly interacts with proteins that play roles in fat metabolism. Peroxisome Proliferator Activator Proteins (PPARs) are transcription factors are found in different tissues such as liver, brown adipose tissues. PPAR family proteins have 3 isoforms in mammalians and regulates fat and glucose metabolism in the body. Circadian clock genes work in oscillation organization. Disrupted night sleep, exposure excess white light, prolonged working hours directly alters the circadian clock rhythm. Altered circadian clock gene regulations changes the glucose and fat metabolism by interrupting Peroxisome Proliferator Activator Proteins (Seo S. H. 2019; Mahmoud, A. 2022).

### 1.2.3 Sedentary Lifestyle

One of the most important environmental factors increasing obesity in childhood and adulthood is the sedentary lifestyle. Sedentary lifestyle and cardiovascular diseases are

shown comorbidity and risk is developed among women patients. According to Centers for Disease Control (CDC) the in the United States the regions that have higher obesity risk also shown that people have more inactive daily life in 2010 Behavioral Risk Factor Surveillance (CDC, 2023). Similar results are shown in different years but also cardiovascular disease risks and mortality among women. Because obesity can be comorbid with hypertension, hyper dyslipidemia, hyper blood sugar, heart diseases the mortality risk is folded in inactive lifestyle (Barnes, A S. 2012).

### 1.2.4 Socioeconomic Status

One of the important factors in the prevalence of the obesity is the socioeconomic status of the individuals and development of the countries. The accessing of healthy foods, healthy diet, active lifestyle, stable sleep cycle, education, race is highly related with obesity risk. Researches show that, individuals who have lover income or lower education level is correlated with development of obesity risk (Anekwe, C. V. 2020). In addition, beside socioeconomic status and education, the inability of certain minority groups to benefit from equal rights with others in health care system and many social issues in many populations also causes risks together with the stress factor it causes. Considering all these together, in addition to improving health systems, providing income equality, increasing access to healthy food and education are very important in reducing the risks of obese society in order to raise individuals who choose wellness as a lifestyle (Anekwe, C. V. 2020; Mayor, S. 2017).

## 1.3 Genetic Factors

### 1.3.1 Monogenic Non-Syndromic Obesity

The prevalence of obesity is increasing in Western and developing countries. In addition to various causes of obesity, there is also a non-syndromic monogenic obesity also called as Mendelian obesity. Mendelian non-syndromic obesity occurs due to variations mutations in a single gene which has role on energy intake signaling pathway also called as

leptin/melanocortin pathway. Mendelian non syndromic obesity has a 5% distribution among others. This spread, which is also referred to as monogenic, occurs due to the mutation in the genes *LEP/LEPR/MC4R/POMC/PC1* (Tirthani, E. 2023; Ranadive, S. 2008).

Monogenic non syndromic obesity was revealed with single mutations in mice. Candidate gene approaches provided information with homologous genes for human obesity via knock-out mice models (Ranadive, S. 2008; Chung, W. K. 2012).

The energy intake and energy expenditure of the body begin with the signal pathways coming to the hypothalamus. Leptin released from adipose tissue binds to the Leptin receptor. Similarly, insulin is released by beta cells in the pancreas and first associates with the insulin receptor. The leptin receptor and insulin receptors are located on pro-opiomelanocortin (POMC) neural cells. POMC signaling pathways provide the release of alpha MSH hormone. Alpha MSH signals are released to stop energy intake. Similarly, in the state of satiety, it binds to the leptin receptor and causes inhibition of agouti-related neuropeptide (AgRP) signals, which cause the transmission of hunger signals. Agouti-related neuropeptide (AgRP) signals and neuropeptide Y (NPY) signals are expressed by AgRP/NPY neurons at higher rates in order to increase energy intake in the fasting state. These two signals are activated when more energy is required in the body by decreasing leptin/insulin level in circulating blood by grehlin hormone which act as an orexigenic hormone. In general, mutations in the genes that encodes proteins related with leptin/melanocortin pathway results obesity. There are several families which has heterogenous mutations in leptin genes resulted as overweight members of the family. Leptin mutations also affects the thyroid hormones (Chung, W. K. 2012).

### 1.3.2 Syndromic Obesity

Syndromic obesity is a form of obesity that usually occurs with developmental delay and is noticed at early ages. It is stated that it occurs with the presence of one or more mutations in the leptin/melanocortin pathway. Syndromic obesity often occurs in conjunction with other diseases; hyperphagia, cognitive dysfunctions, abnormalities in organ level and developmental disorders. Prader Willi, Bardet- Biedl, Alstrom and WAGR are most common

forms of syndromic obesity. Prader Willi the most common syndromic obesity form shows in 1 in 10000 to 15000 births and mostly caused by deletions in the chromosome. Facial and limb discrepancy, thyroid hormone dysfunctions, behavioral abnormalities are also observed.

Bardet- Biedl is the second most common syndromic obesity form that affects 1 in 13500 to 15000 individuals (Huvenne, H. 2016).

### 1.3.3 Oligogenic Obesity

Similar with the monogenic obesity, oligogenic obesity is also associated with leptin melanocortin pathway related gene mutations. However, oligogenic obesity is correlated with environmental conditions additional to genetic factors. Oligogenic obesity prevalence is 2-3% among the adulthood and childhood obesity cases (Huvenne, H. 2016).

### 1.3.4 Polygenic Obesity

Lots of study implied that, common obesity is polygenic mostly related with small effects of each gene interacts with the environments and other alleles. This association complicates the understanding of each genes and their effects on obesity. Mode of inheritance, either monogenic dominant or recessive clarifies small group of obese population with additional phenotypic traits; however, polygenic effect of alleles and their interaction with the other alleles and environment still has a derangement**.** While monogenic obesity is explained by mutations in certain genes, polygenic obesity explains that small effects of alleles in hundreds of different genes cause the disease when they found in the individuals. While the presence of one allele alone does not reveal obesity, the presence of dozens of risk alleles may increase the risk of the disease (Hinney, A. 2008).

Candidate gene studies, mostly case-control studies, animal models, and to a lesser extent family-twin studies have made significant contributions to the understanding of monogenic obesity to date. Polygenic obesity is understood through genome-wide research studies and candidate gene studies. Genome-wide association studies (GWAS) are the study of detecting the alleles (SNPs) that is associated a disease or trait by scanning the entire

genome of individuals. GWAS require large populations in terms of 10000 to millions with the specific disease or trait. Throughout the study, thousands of individual genomes are scanned and most frequently encountered SNPs are detected and mapped. Revealing risk alleles for each person has been significantly promising in complex diseases (Uffelmann, E. 2023).

### 1.3.5 Epigenetic Factors

Epigenetic factors both include altering gene expressions and also environmental factors in increasing rate of obesity. DNA methylation one of the epigenetic factors plays role in obesity alters leptin and adiponectin levels which regulates the satiety and adiposity regulation in the body (Tirthani, E. 2023). The other crucial epigenetic factor is histone modification which alters gene expression by changing the affinity of transcription factors on the DNA. Noncoding regions which affect the transcription factor binding site, enhancer or promoter region alters the affinity of transcription factors in three-dimensional way and changes the protein synthesis (Herrera, B. 2011).

Beside the altering transcription, there are several factors also determines the obesity risk in individuals. Studies revealed that exposure of heavy metals, chemicals, lifestyle like exercise smoking and alcohol usage, dietary factors of parents are also affecting the obesity risk of newborns (Mahmoud, A. 2022).

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## 1.4 Polygenic Risk Score

The polygenic risk score expresses the numerical effect of the risk alleles affecting the disease on the individual. Polygenic risk score approach can be used to measure the effects of many alleles on the same disease after genome-wide association studies and is a method under development (Choi ,W. 2020).

Polygenic risk score mostly calculated by sum of risk alleles of an individual that is weighted with the effect size in terms of beta value or Z-score from GWAS summary statistics of related phenotype. There are lots of applications in the field especially on Type

2 Diabetes, Schizophrenia, cardiovascular disease risk detection. There are several studies implied that, polygenic risk score calculation will be prior method in disease assessment (Choi ,W. 2020).

## 1.5 Hypothesis and Aims of the Thesis

There are several risk factors increasing the obesity in populations. One of the hypotheses is that, polygenic effect of the obesity in adulthood and childhood are different. The aim of this thesis is to show overlap genetic risk factors for childhood and adulthood obesity via bioinformatic tools and calculation of polygenic risk score population in mixed groups. In addition, to analyze candidate gene and GWAS studies for childhood obesity, identify candidate genes and their variants, and develop a new genetic test panel that can be broadscale for predicting childhood obesity related variants.

# CHAPTER 2

# MATERIALS AND METHODS

## 2.1 Data Collection

All data in the analyzes were examined under 4 different headings The study is spitted into subheadings of the mentioned studies are as follows:

2.1 Data Collection

2.1.1 Listing childhood obesity related SNPs

2.1.2 Listing adulthood obesity related SNPs

2.2 Identification of childhood and adulthood obesity related SNPs and interactions

2.2.1 SNP Annotations

2.2.2 Structural interaction (3D) of SNPs and genes

2.2.3 Linkage Disequilibrium (LD) Analysis

2.3 Identification of childhood and adulthood obesity related genes functions

2.3.1 Gene Annotations

2.3.2 Pathway Analysis

2.4 Protein -Protein Interaction Network Analysis

In this thesis, first of all GWAS Catalog (URL1) is used to reach out listed obesity related variants included in GWAS studies in childhood obesity and adulthood obesity. Variants selected and listed in Appendix A for childhood related obesity and in Appendix B for adulthood related obesity as threshold $p < 1\times10^{-6}$ (Sollis, E. 2023).

Childhood obesity related variants were listed with additional informations. In order to make the study more inclusive, no population discrimination was made. As listed in Appendix A (partially represented), all data of Hispanic, European, African, North/South American, and East Asian ancestry, North American, Australian, and European and Korean

populations are included. Position of the variants, beta values, population information, mapped genes, additional traits are added as an additional information (Sollis, E. 2023).

In Appendix B (partially represented), adulthood related SNPs generated from Hispanic, Latin American, Asian, European, Native American, Oceanian, Eastern African, American or Afro-Caribbean populations. From GWAS Catalog variants have value $p < 1\times10^{-6}$ are included. Additional information as position of the variants, beta values, population information, mapped genes, additional traits are also included (Sollis, E. 2023).

## 2.2 Identification of Genes and Variants Associated with Childhood and Adulthood Obesity

### 2.2.1 SNP Annotations

First analysis was SNP annotation for childhood and adulthood obesity related variants. Fort this analysis SNP Nexus annotation tool (URL2) was used (Oscanoa, J. 2018). Threshold $p < 1\times10^{-8}$ was used for the annotation and shown in results Table 1.1.1.

Out of 1014 childhood related variants from GWAS Catalog, 33 of variants that have p value $p < 1\times10^{-8}$ are listed in Table 1.1.1. Variants, SNP database tool representation (URL3) chromosome number and position, reference allele, altered and minor allele, and frequency of the minor allele informations are shown in table. Genetic coordination informations are provided from gnomAd Browser tool in SNP Nexus analysis tool (URL4).

For adulthood obesity related variants same analysis applied. Table 1.1.2 partially shows position of the variants, beta values, population information, mapped genes. Additional traits are also included. table is represented in Appendix B partially. Detailed SNP annotations are implemented in Table 1.2.3.

In Table 1.2.2, overlapped genes, upstream and downstream nearest genes, distances and SNP annotations are listed. SNP Nexus Annotation tool provides this analysis from Consensus CDC database (URL5).

In order to understand epigenetic effects of the SNPs, regulatory element analysis via RegBuild, ENCODE on SNP Nexus tool are performed **(**Data is not shown**).**

Same analyses are applied for adulthood related SNPs. Out of 274 SNPs that have p value $p < 1\times10^{-6}$ , 142 variants that have $p < 1\times10^{-8}$ are selected and listed in Table 1.2.1. Detailed frequency distributions and SNP annotations are shown in Table 1.2.2 and Table 1.2.3. Figure 1.1 and Figure 1.2 represents the karyotype analysis.

### 2.2.2 3D SNP Interactions

Due to most of the structural variants are not located in the coding regions of the genes, several additional analyses are required to understand the effect of the specific variants. As an example, some structural variants are located on promoter, enhancer or transcription factor binding site which changes the affinity of specific proteins in transcription. In addition, several variants may lead to change in histone modification due to 3D interactions of the other specific gene regions.

3D SNP Structural analysis was applied in 3D SNP (URL6) tool which provides information about three-dimensional interaction with chromatin structures, regulatory and/or enhancer regions of the genes (Quan, C. 2022).

### 2.2.3 Linkage Analysis

Linkage analysis applied in 3D SNP analysis tool (URL6). Linkage analysis is the powerful method to understand correlation of variants at different locus that might be inherited in a linkage in specific populations. LD Analysis provide information with $R^2$ the correlation coefficient within 0 to 1 and D' within 0 to 1. $R^2$ >0.8 is selected in the analysis.

## 2.3 Identification of childhood and adulthood obesity related genes functions

### 2.3.1 Pathway Analysis

In order to understand the affected metabolic pathways, pathway analysis applied in Reactome Database (URL7). Reactome Database provide information to visualize signaling molecules and pathways, proteins involved in metabolic pathways, biological functions, and gene annotations. In order to understand the difference of those SNPs related with childhood and adulthood obesity in metabolic pathways, pathway analysis is applied (Griss, J. 2017).

## 2.4 Protein – Protein Interaction Network Analysis

Protein – protein network analysis provides additional information about protein interaction on the pathways. Protein network analysis is an analysis that helps us to map proteins that are not genetically interacting but interact on the metabolic pathway, have co-expression, gene fusion. If none of these, proteins those are not interacted but have similar effects that found in the same study are mapped. STRING Protein-Protein Interaction Networks Functional Enrichment Analysis Tool (URL8) is used to generate the interaction network. The proteins those encoded by childhood obesity related SNPs overlapped genes and the proteins those encoded by adulthood obesity related SNPs overlapped genes are mapped within these 2 groups. Most phenotype related protein network analysis are also applied based on scores. Scores implied only the confidence of the network (Szklarczyk, D. 2023).

## 2.5 Polygenic Risk Score Calculation

For variants affecting childhood obesity, the polygenic risk score was calculated as sum of the finding of susceptible variants multiplied by the estimated effect size (beta value

from the GWAS summary statistical result) the probability of finding each variant. The basic model applied to understand the importance of each variant and co-existence of each susceptible variants (Choi ,W. 2020).

Individuals' obesity risk profiles are calculated using the weighted sum of risk alleles. Such a model is one of the fundamental models used to calculate the polygenic risk score of a phenotype. There are more complex methods in the literature (Choi ,W. 2020).

The weights of the model are the effect sizes of each gene variant that are determined by p-value thresholding using GWAS (genome-wide association studies). If an individual genotype consists of risk alleles related to obesity, then the number of risk alleles is multiplied by the effect size. All variants that are related to the risk of obesity are taken into account in the polygenic risk score model (Choi ,W. 2020). The calculation formula is stated below:

$$S = \sum_{1}^{n} \beta_n w$$

S represents the polygenic risk score of individuals, beta is the effect size of variants, and w is the number of risk alleles in the individual's genotype, which is a set of 0, 1, 2. n is the number of risk variants that were taken into account in our model.

# CHAPTER 3

# RESULTS

## 3.1 Data Collection

In table 3.1.1, childhood obesity related SNPs that have $p < 1\times10^{-8}$ are listed from GWAS Catalog. Variation ID, dbSNP ID, chromosome**,** position, reference allele, altered allele, minor allele, and minor allele global frequency is represented in Table 1.1.1

Table 3.1 Childhood Obesity Related SNPs from GWAS Catalog

| **Variation ID** | **dbSNP** | **Chromosome** | **Position** | **REF Allele** | **ALT Allele (IUPAC)** | **Minor Allele** | **Minor Allele Global Frequency** |
|---|---|---|---|---|---|---|---|
| rs10493544 | rs10493544 | 1 | 74518151 | T | C | C | 0.288139 |
| rs12075 | rs12075 | 1 | 159205564 | G | A | G | 0.459465 |
| rs539515 | rs539515 | 1 | 177919890 | A | Y | C | 0.194688 |
| rs28461806 | rs28461806 | 10 | 43260306 | T | C | None | None |
| rs10830963 | rs10830963 | 11 | 92975544 | C | G | G | 0.260184 |
| rs3741298 | rs3741298 | 11 | 116786845 | C | T | C | 0.350439 |
| rs7132908 | rs7132908 | 12 | 49869365 | G | A | A | 0.251997 |
| rs494558 | rs494558 | 13 | 110276815 | C | T | C | 0.164337 |
| rs10131141 | rs10131141 | 14 | 20793574 | C | T | C | 0.314696 |
| rs3783637 | rs3783637 | 14 | 54881400 | C | T | T | 0.204273 |
| rs17104363 | rs17104363 | 14 | 67472766 | T | C | C | 0.116214 |
| rs8037818 | rs8037818 | 15 | 32635275 | C | T | C | 0.256789 |
| rs8040868 | rs8040868 | 15 | 78618839 | T | C | C | 0.328474 |
| rs56094641 | rs56094641 | 16 | 53772541 | A | K | G | 0.228834 |
| rs74583214 | rs74583214 | 16 | 90044390 | C | T | T | 0.026558 |
| rs61744862 | rs61744862 | 17 | 17164868 | G | A | A | 0.004992 |

Cont. on the next page

Cont. of Table 3.1

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| rs6567160 | rs6567160 | 18 | 60161902 | T | C | C | 0.223243 |
| rs12104221 | rs12104221 | 19 | 3797102 | C | T | T | 0.156550 |
| rs7595 | rs7595 | 19 | 54193224 | T | C | C | 0.251797 |
| rs7579427 | rs7579427 | 2 | 631183 | C | W | C | 0.122005 |
| rs73175262 | rs73175262 | 2 | 11618305 | G | A | A | 0.014377 |
| rs4077678 | rs4077678 | 2 | 24899971 | C | G | C | 0.450879 |
| rs114670539 | rs114670539 | 2 | 206199611 | C | T | T | 0.017173 |
| rs6044834 | rs6044834 | 20 | 17455828 | T | G | G | 0.100240 |
| rs6025590 | rs6025590 | 20 | 57495449 | A | G | A | 0.266374 |
| rs2823615 | rs2823615 | 21 | 16110813 | A | T | T | 0.267372 |
| rs12636651 | rs12636651 | 3 | 46240900 | T | C | C | 0.404553 |
| rs3733402 | rs3733402 | 4 | 186236880 | G | M | G | 0.395367 |
| rs2206277 | rs2206277 | 6 | 50830813 | C | T | T | 0.211661 |
| rs11974269 | rs11974269 | 7 | 21108059 | A | C | C | 0.209465 |
| rs16933006 | rs16933006 | 9 | 15335916 | A | C | C | 0.175519 |
| rs1443438 | rs1443438 | 9 | 97787746 | T | M | T | 0.207468 |

In Table 3.1 data are gathered on SNP Nexus from 1000 Genome project.

Table 3.2 Adulthood Obesity Related SNPs from GWAS Catalog

| **Variation ID** | **dbSNP** | **Chromosome** | **Position** | **REF Allele** | **ALT Allele (IUPAC)** | **Minor Allele** | **Minor Allele Global Frequency** |
|---|---|---|---|---|---|---|---|
| rs3765964 | rs3765964 | 1 | 8974362 | G | M | A | 0.460064 |
| rs10732279 | rs10732279 | 1 | 19978572 | C | T | C | 0.165735 |
| rs1886748 | rs1886748 | 1 | 38868103 | C | A | A | 0.313099 |
| rs11208659 | rs11208659 | 1 | 65513597 | T | C | C | 0.193291 |
| rs3101336 | rs3101336 | 1 | 72285502 | T | C | T | 0.324880 |
| rs2568958 | rs2568958 | 1 | 72299433 | G | M | G | 0.324481 |

Table 3.1 and 3.2 are represents the childhood and adulthood related variants both analyzed in SNP Nexus Annotation tool. The data is provided from 1000 Genome Project in the database. In the table 3.2, adulthood obesity related SNPs are partially shown (The 1000 Genomes Project Consortium. 2011).

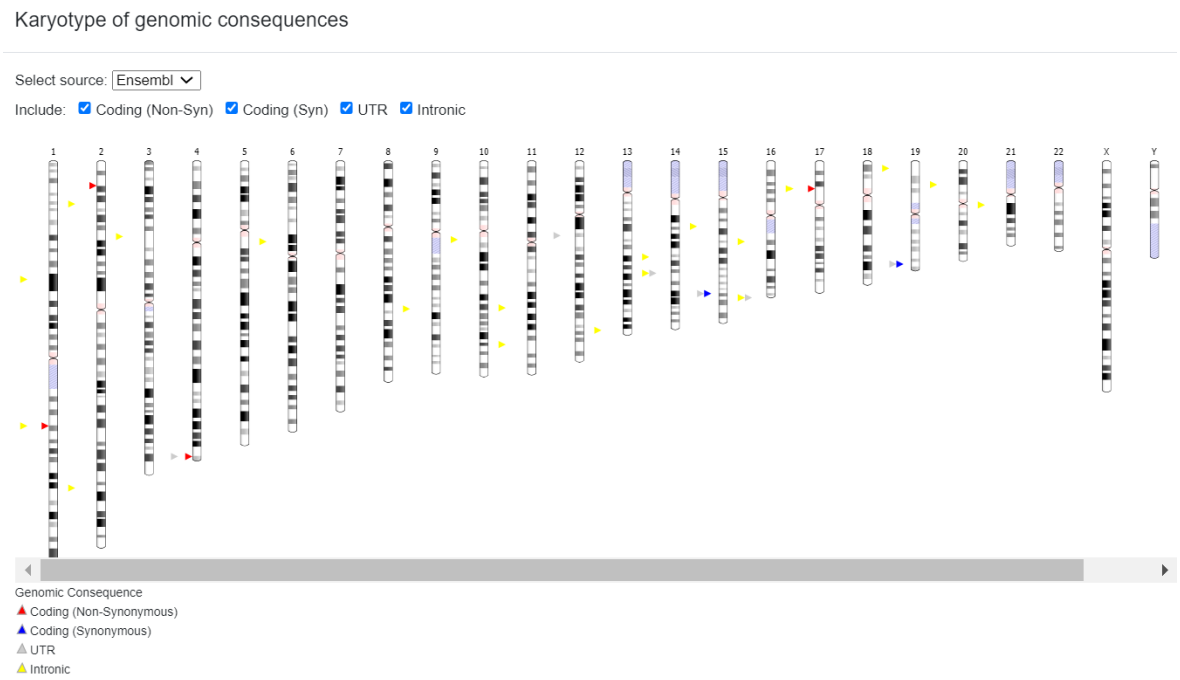


Figure 3.1 Distribution of childhood obesity related SNPs on human chromosomes

Each SNPs on chromosomes are represented in Figure 3.1 for childhood obesity related variants. Coding non-synonymous, coding synonymous, UTR and intronic SNPs are all shown in autosomal chromosomes. The analysis is provided by SNP Nexus Annotation tool (Oscanoa, J. 2018).

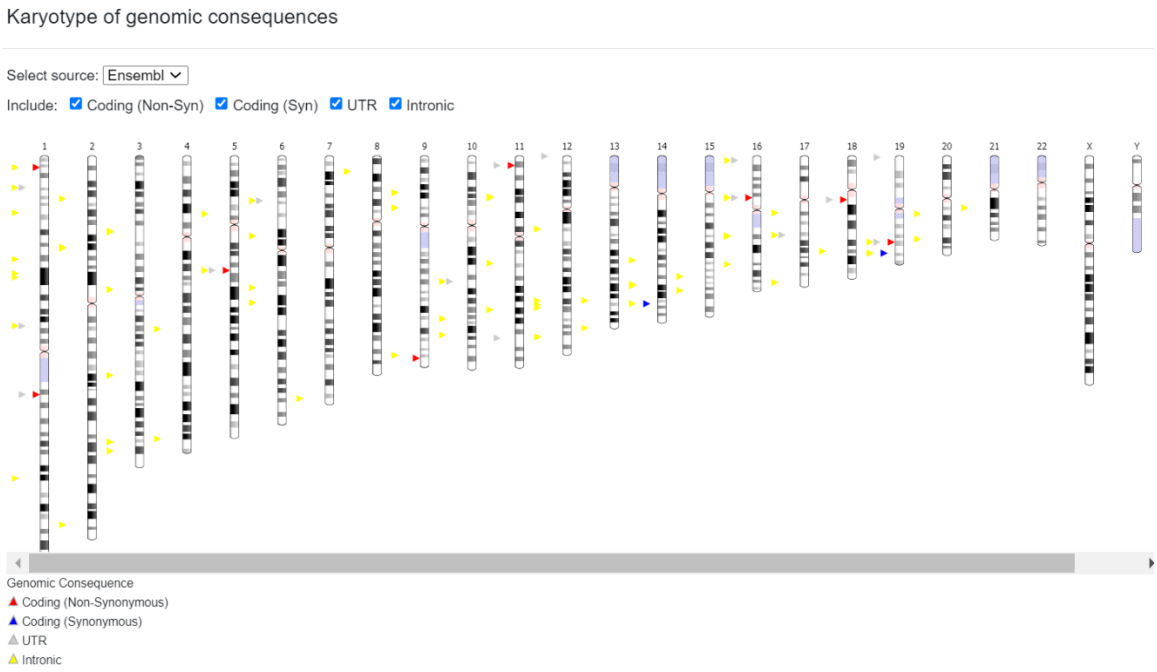


Figure 3.2 Distribution of adulthood obesity related SNPs on human chromosomes

Each SNPs on chromosomes are represented in figure 3.2 adulthood related obesity variants. SNPs show scattered on chromosomes. Coding non-synonymous, coding synonymous, UTR and intronic SNPs are all shown in autosomal chromosomes. The analysis is provided by SNP Nexus Annotation tool (Oscanoa, J. 2018).

## 3.2 Identification of childhood and adulthood obesity related SNPs and interactions

### 3.2.1 SNP Annotations

SNP annotation provides additional information about SNP location and function on genes. Some of the variants might affect the protein coding. Intronic, upstream, downstream, synonymous, nonsynonymous SNPs are shown (Oscanoa, J. 2018).

Table 3.3 Childhood obesity related SNPs allele frequency

| Variation ID | AFR Frequency | AMR Frequency | EAS Frequency | EUR Frequency | SAS Frequency | Chromosome | Position | Overlapped Gene |
|---|---|---|---|---|---|---|---|---|
| rs10493544 | 0.108900 | 0.386200 | 0.076400 | 0.554700 | 0.404900 | chr1 | 74518151 | FPGT-TNNI3K |
| rs12075 | 0.981100 | 0.538900 | 0.077400 | 0.602400 | 0.359900 | chr1 | 159205564 | CADM3-AS1, ACKR1 |
| rs539515 | 0.276900 | 0.190200 | 0.145800 | 0.183900 | 0.148300 | chr1 | 177919890 | None |
| rs28461806 | 0 | 0 | 0 | 0 | 0 | chr10 | 43260306 | RASGEF1A |
| rs10830963 | 0.027200 | 0.193100 | 0.422600 | 0.288300 | 0.426400 | chr11 | 92975544 | MTNR1B |
| rs3741298 | 0.633900 | 0.572000 | 0.591300 | 0.765400 | 0.666700 | chr11 | 116786845 | ZPR1 |
| rs7132908 | 0.108900 | 0.255000 | 0.230200 | 0.356900 | 0.357900 | chr12 | 49869365 | FAIM2 |
| rs494558 | 0.680800 | 0.917900 | 0.770800 | 0.990100 | 0.894700 | chr13 | 110276815 | COL4A1 |
| rs10131141 | 0.599100 | 0.701700 | 0.753000 | 0.615300 | 0.792400 | chr14 | 20793574 | None |
| rs3783637 | 0.104400 | 0.154200 | 0.423600 | 0.087500 | 0.268900 | chr14 | 54881400 | GCH1 |
| rs17104363 | 0.090800 | 0.090800 | 0.140900 | 0.143100 | 0.115500 | chr14 | 67472766 | TMEM229B |
| rs8037818 | 0.829000 | 0.819900 | 0.667700 | 0.747500 | 0.646200 | chr15 | 32635275 | ARHGAP11A, AC123768.5 |
| rs8040868 | 0.353300 | 0.279500 | 0.354200 | 0.416500 | 0.212700 | chr15 | 78618839 | CHRNA3 |
| rs56094641 | 0.054500 | 0.242100 | 0.167700 | 0.434400 | 0.306700 | chr16 | 53772541 | FTO |
| rs74583214 | 0.004500 | 0.015900 | None | 0.083500 | 0.032700 | chr16 | 90044390 | GAS8, URAHP |
| rs61744862 | 0.018900 | None | None | None | None | chr17 | 17164868 | MPRIP |
| rs6567160 | 0.220100 | 0.131100 | 0.182500 | 0.239600 | 0.318000 | chr18 | 60161902 | None |
| rs12104221 | 0.100600 | 0.373200 | 0.177600 | 0.115300 | 0.099200 | chr19 | 3797102 | MATK |
| rs7595 | 0.143700 | 0.309800 | 0.519800 | 0.173000 | 0.161600 | chr19 | 54193224 | TSEN34 |
| rs7579427 | 0.904700 | 0.861700 | 0.913700 | 0.826000 | 0.870100 | chr2 | 631183 | None |
| rs73175262 | 0.053000 | 0.001400 | 0.001000 | None | None | chr2 | 11618305 | GREB1 |
| rs4077678 | 0.910000 | 0.351600 | 0.421600 | 0.426400 | 0.459100 | chr2 | 24899971 | ADCY3 |
| rs114670539 | 0.003000 | 0.040300 | None | 0.048700 | 0.005100 | chr2 | 206199611 | GPR1 |
| rs6044834 | 0.173200 | 0.103700 | 0.005000 | 0.145100 | 0.051100 | chr20 | 17455828 | PCSK2 |
| rs6025590 | 0.888000 | 0.683000 | 0.656700 | 0.587500 | 0.790400 | chr20 | 57495449 | None |
| rs2823615 | 0.394900 | 0.229100 | 0.071400 | 0.304200 | 0.286300 | chr21 | 16110813 | MIR99AHG |
| rs12636651 | 0.432700 | 0.340100 | 0.592300 | 0.261400 | 0.366100 | chr3 | 46240900 | CCR3 |
| rs3733402 | 0.775300 | 0.589300 | 0.682500 | 0.522900 | 0.388500 | chr4 | 186236880 | KLKB1 |
| rs2206277 | 0.127100 | 0.344400 | 0.234100 | 0.181900 | 0.239300 | chr6 | 50830813 | TFAP2B |
| rs11974269 | 0.284400 | 0.149900 | 0.152800 | 0.169000 | 0.250500 | chr7 | 21108059 | None |
| rs16933006 | 0.070300 | 0.089300 | 0.327400 | 0.142100 | 0.256600 | chr9 | 15335916 | None |
| rs1443438 | 0.869900 | 0.694500 | 0.868100 | 0.662000 | 0.813900 | chr9 | 97787746 | PTCSC2 |

Table 3.3 represents allelic frequency and positions of related SNPs.

Overlapped genes, chromosomes, allelic frequency are shown on table. The analysis applied in SNP Nexus annotation tool. The data is provided by Ensembl (URL9).

Table 3.4 Overlapped genes, nearby genes and SNP annotations of childhood related variants

| Variation ID | Chromosome | Position | Overlapped Gene | Type | Annotation |
|---|---|---|---|---|---|
| rs10493544 | chr1 | 74518151 | FPGT-TNNI3K, TNNI3K | protein_coding | intronic |
| rs12075 | chr1 | 159205564 | CADM3-AS1, ACKR1 | antisense | non-coding intronic |
| rs539515 | chr1 | 177919890 | None | None | None |
| rs28461806 | chr10 | 43260306 | RASGEF1A | protein_coding | intronic |
| rs10830963 | chr11 | 92975544 | MTNR1B | protein_coding | intronic |
| rs3741298 | chr11 | 116786845 | ZPR1 | protein_coding | 5upstream, intronic, 3downstream, non-coding intronic |
| rs7132908 | chr12 | 49869365 | FAIM2 | protein_coding | 3utr,3downstream |
| rs494558 | chr13 | 110276815 | COL4A1 | protein_coding | non-coding intronic, intronic |
| rs10131141 | chr14 | 20793574 | None | None | None |
| rs3783637 | chr14 | 54881400 | GCH1 | protein_coding | non-coding intronic, intronic |
| rs17104363 | chr14 | 67472766 | TMEM229B | protein_coding | 3utr, intronic, 3downstream |
| rs8037818 | chr15 | 32635275 | ARHGAP11A, AC123768.5 | protein_coding | intronic, non-coding intronic |
| rs8040868 | chr15 | 78618839 | CHRNA3 | protein_coding | coding syn, 5 utr, non-coding, 3downstream |
| rs56094641 | chr16 | 53772541 | FTO | protein_coding | non-coding intronic, intronic |

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Cont. of Table 3.4

| | | | | | |
|---|---|---|---|---|---|
| rs74583214 | chr16 | 90044390 | URAHP | transcribed_unprocessed_pseudogene | non-coding intronic |
| rs61744862 | chr17 | 17164868 | MPRIP | protein_coding | coding nonsyn, intronic, 5upstream |
| rs6567160 | chr18 | 60161902 | None | None | None |
| rs12104221 | chr19 | 3797102 | MATK | protein_coding | intronic, non-coding intronic |
| rs7595 | chr19 | 54193224 | TSEN34 | protein_coding | non-coding, coding syn, 3downstream |
| rs7579427 | chr2 | 631183 | None | None | None |
| rs73175262 | chr2 | 11618305 | GREB1 | protein_coding | coding nonsyn, 3downstream |
| rs4077678 | chr2 | 24899971 | ADCY3 | protein_coding | intronic |
| rs114670539 | chr2 | 206199611 | GPR1 | protein_coding | intronic |
| rs6044834 | chr20 | 17455828 | PCSK2 | protein_coding | intronic |
| rs6025590 | chr20 | 57495449 | None | None | None |
| rs2823615 | chr21 | 16110813 | MIR99AHG | lincRNA | non-coding intronic |
| rs12636651 | chr3 | 46240900 | CCR3 | protein_coding | 5upstream, intronic |
| rs3733402 | chr4 | 186236880 | KLKB1 | protein_coding | coding nonsyn\|nonsyn, coding *nonsyn\|nonsyn, non-coding |
| rs2206277 | chr6 | 50830813 | TFAP2B | protein_coding | intronic |
| rs11974269 | chr7 | 21108059 | None | None | None |
| rs16933006 | chr9 | 15335916 | None | None | None |
| rs1443438 | chr9 | 97787746 | PTCSC2 | lincRNA | non-coding intronic |

Table 3.4 represents childhood obesity related variants and SNP annotations of the variants.

Variants which do not represent any overlap with the specific gene may have upstream and downstream genes on the DNA. rs539515 has *LINC01741* upstream that encodes lincRNA

and *SEC16B* downstream protein coding gene. rs10131141 variant has downstream *RNASE1* protein coding gene. rs6567160 variant has *AC090771.2* encoding lincRNA and *RNU4-17P* downstream that encodes snRNA. rs7579427 has upstream *AC093326.1* gene that encodes lincRNA and *TMEM18* protein coding gene. rs6025590 variant also has downstream *CTCFL* protein encoding gene. rs11974269 have both upstream and downstream AC080068.1 and *RN7SL542P* lincRNA and miscellaneous RNA.

Table 3.5 Adulthood related obesity SNPs

| **Variation ID** | **dbSNP** | **Chromosome** | **Position** | **REF Allele** | **ALT Allele (IUPAC)** | **Minor Allele** | **Minor Allele Global Frequency** |
|---|---|---|---|---|---|---|---|
| rs3765964 | rs3765964 | 1 | 8974362 | G | M | A | 0.460064 |
| rs10732279 | rs10732279 | 1 | 19978572 | C | T | C | 0.165735 |
| rs1886748 | rs1886748 | 1 | 38868103 | C | A | A | 0.313099 |
| rs11208659 | rs11208659 | 1 | 65513597 | T | C | C | 0.193291 |
| rs3101336 | rs3101336 | 1 | 72285502 | T | C | T | 0.324880 |
| rs2568958 | rs2568958 | 1 | 72299433 | G | M | G | 0.324481 |
| rs7531118 | rs7531118 | 1 | 72371556 | T | C | C | 0.285343 |
| rs1993709 | rs1993709 | 1 | 72372846 | A | G | A | 0.095847 |
| rs1514177 | rs1514177 | 1 | 74525718 | C | G | G | 0.406749 |
| rs1514174 | rs1514174 | 1 | 74527379 | C | T | T | 0.337660 |
| rs17381664 | rs17381664 | 1 | 77582646 | T | C | C | 0.185703 |
| rs17024258 | rs17024258 | 1 | 109604699 | C | T | T | 0.031550 |
| rs13294 | rs13294 | 1 | 150512511 | G | W | A | 0.266573 |
| rs12042360 | rs12042360 | 1 | 159739035 | G | W | A | 0.262181 |
| rs11588887 | rs11588887 | 1 | 159747372 | G | A | A | 0.264976 |
| rs633715 | rs633715 | 1 | 177883445 | T | C | C | 0.145168 |
| rs1329428 | rs1329428 | 1 | 196733680 | C | T | T | 0.482428 |
| rs10919774 | rs10919774 | 1 | 199938588 | A | G | G | 0.044928 |
| rs2605100 | rs2605100 | 1 | 219470882 | A | G | A | 0.191094 |
| rs2116830 | rs2116830 | 10 | 76886778 | G | T | T | 0.070288 |
| rs11599750 | rs11599750 | 10 | 100045685 | C | T | T | 0.335064 |
| rs10509957 | rs10509957 | 10 | 112294225 | G | A | G | 0.414337 |
| rs9325542 | rs9325542 | 10 | 113217610 | A | G | G | 0.291334 |
| rs11042023 | rs11042023 | 11 | 8640969 | T | C | T | 0.474840 |

Table 3.5 represents adulthood obesity related variants, reference allele, chromosome, position, altered allele, minor allele and minor allele global frequency. The total list includes 142 variants. In Table 3.5 small portion is represented.

Table 3.6 Adulthood related variants SNP annotation

| **Variation ID** | **Chromosome** | **Position** | **Overlapped Gene** | **Type** | **Annotation** | **Nearest Upstream Gene** |
|---|---|---|---|---|---|---|
| rs3765964 | chr1 | 8974362 | CA6 | protein_coding | intronic, coding nonsyn\| nonsyn, non-coding intronic | None |
| rs10732279 | chr1 | 19978572 | PLA2G2A | protein_coding | non-coding intronic, non-coding, intronic | None |
| rs1886748 | chr1 | 38868103 | AL139260.3 | protein_coding | non-coding intronic, intronic | None |
| rs1886748 | chr1 | 38868103 | AL139260.2 | processed_transcript | non-coding intronic | None |
| rs1886748 | chr1 | 38868103 | AL139260.1 | antisense | non-coding intronic | None |
| rs1886748 | chr1 | 38868103 | MYCBP | protein_coding | intronic, non-coding intronic | None |
| rs11208659 | chr1 | 65513597 | LEPR | protein_coding | intronic | None |

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Cont. of Table 3.6

| | | | | | | |
|---|---|---|---|---|---|---|
| rs3101336 | chr1 | 72285502 | None | None | None | NEGR1 |
| rs2568958 | chr1 | 72299433 | None | None | None | NEGR1 |
| rs7531118 | chr1 | 72371556 | None | None | None | RPL31P12 |
| rs1993709 | chr1 | 72372846 | None | None | None | RPL31P12 |
| rs1514177 | chr1 | 74525718 | FPGT-TNNI3K | protein_coding | intronic | None |
| rs1514177 | chr1 | 74525718 | TNNI3K | protein_coding | intronic | None |
| rs1514174 | chr1 | 74527379 | FPGT-TNNI3K | protein_coding | intronic | None |
| rs1514174 | chr1 | 74527379 | TNNI3K | protein_coding | intronic | None |
| rs17381664 | chr1 | 77582646 | AC118549.1 | protein_coding | intronic, non-coding intronic | None |
| rs17024258 | chr1 | 109604699 | GNAI3 | protein_coding | 3utr | None |
| rs17024258 | chr1 | 109604699 | GNAT2 | protein_coding | intronic | None |
| rs13294 | chr1 | 150512511 | ECM1 | protein_coding | coding nonsyn\| nonsyn,non-coding, 3downstream | None |
| rs12042360 | chr1 | 159739035 | None | None | None | CRP |
| rs11588887 | chr1 | 159747372 | None | None | None | CRP |
| rs633715 | chr1 | 177883445 | None | None | None | LINC01741 |

Cont of Table 3.6

| | | | | | | |
|---|---|---|---|---|---|---|
| rs1329428 | chr1 | 196733680 | CFH | protein_coding | intronic, non-coding intronic | None |
| rs10919774 | chr1 | 199938588 | None | None | None | AL445687.2 |
| rs2605100 | chr1 | 219470882 | None | None | None | LYPLAL1-AS1 |
| rs2116830 | chr10 | 76886778 | KCNMA1 | protein_coding | intronic, non-coding intronic, non-coding, 3utr, 3downstream | None |

In table 3.6, adulthood related variants overlapped genes SNP annotation also represented. Variants that do not have overlapped gene have upstream and downstream nerarest genes. The analysis provided the whole results. Processed pseudogene, lincRNA, snRNA, protein coding genes, miRNA, bidirectional promoter lncRNA, miscellaneous RNA are gathered from the analysis**.**

## 3.2.2 SNP interactions

SNP interactions give information of each variant with 3D interacting genes, enhancer, promoter, transcription factor binding site locations in how many different cell types, and total score functionality of this SNP (Quan, C. 2022).

Table 3.7 3D SNP interactions

| Variant ID | Score | 3D interacting gene | Enhancer | Promoter | TFBS | Motif |
|---|---|---|---|---|---|---|
| rs7132908 | 160,56 | BCDIN3D-AS1, AQP2, AQP5, AQP6, ASIC1, BCDIN3, FAIM2, LOC283332, NCKAP5L, RACGAP1, | 70 | 1 | 97 | |
| rs3783637 | 118,25 | GCH1, MIR4308, SAMD4A | 1 | 86 | 22 | 1 |

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Cont. of Table 3.7

| | | | | | | |
|---|---|---|---|---|---|---|
| rs6025590 | 106,12 | CTCFL, MTRNR2L3, PCK1, RAE1, RBM38, | 17 | 3 | 102 | |
| rs3741298 | 49,15 | APOA5, APOA1, APOA4, APOC3, BUD13, PAFAH1B2, PCSK7, RNF214, SIK3, TAGLN, ZNF259 | 59 | 9 | | |
| rs8040868 | 32,53 | CHRNB4, CHRNA3, CHRNA5, HYKK, WDR61 | 44 | 4 | 9 | 2 |
| rs56094641 | 18,68 | RPGRIP1L, FTO, IRX3, IRX5 | 36 | 1 | | |
| rs28461806 | 14,89 | FXYD4, HNRNPF, RASGEF1A, ZNF487P | 28 | | | 1 |
| rs7595 | 14,57 | MBOAT7, CNOT3, LENG1, LILRA3, LILRA5, LILRA6, LILRB2, LILRB3, LILRB5, MIR4752, RPF31, RPS9, TFPT, TMC4, TSEN34 | 31 | | | 1 |
| rs494558 | 9,87 | COL4A2, COL4A1 | 18 | | | |
| rs12075 | 6,51 | LOC100131825, AIM2, CADM3, DARC, DUSP23, FCER1A, OR10J3 | 7 | 3 | 8 | |
| rs114670539 | 5,41 | SNORD51, EEF1B2, GCSHP3, GPR1, INO80D, NDUFS1, SNORA41, SNORD51, ZDBF2, | 3 | | | 2 |
| rs10131141 | 4,86 | EDDM3B, ANG, ECRP, EDDM3A, OR6S1, RNASE1, RNASE2, RNASE3, RNASE4 | 6 | | | 2 |
| rs73175262 | 4,36 | MIR4429, E2F6, GREB1, LPIN1, NTSR2, | 2 | | 2 | 1 |
| rs3733402 | 2,8 | FLJ38576, CYP4V2, KLKB1 | 1 | | | |
| rs12636651 | 2,68 | CCR3, CCR1, CCR2, CCR5, CXCR6 | 4 | | | |
| rs7579427 | 2,59 | | | | | 2 |
| rs11974269 | 2,28 | | 7 | | | |
| rs12104221 | 2,2 | APBA3, ATCAY, MATK, MRPL54, NMRK2, PIP5K1C, RAX2, TJP3, ZFR2, | 2 | | | |
| rs4077678 | 1,9 | DNAJC27, ADCY3, DNAJC27-AS1, EFR3B | | | | |
| rs17104363 | 1,89 | PLEK2, COPS3, FLCN, MPRIP, NT5M, PLD6 | 2 | | | |
| rs6567160 | 1,76 | | 3 | | | |

Cont. on the next page

Cont. of Table 3.7

| | | | | | | |
|---|---|---|---|---|---|---|
| rs10830963 | 1,71 | MTNR1B | 2 | | 2 | |
| rs1443438 | 1,59 | FOXE1, XPA | 1 | | | |
| rs16933006 | 1,52 | TTC39B, SNAPC3 | | | | |
| rs2823615 | 1,42 | LINC00478 | | | | |
| rs2206277 | 1,31 | TFAP2B, TFAP2D | 2 | | | |
| rs61744862 | 1,11 | FLCN | 4 | | | |
| rs10493544 | 1,04 | C1orf173 | 1 | | | |
| rs539515 | 0,86 | ASTN1 | 1 | | | |
| rs6044834 | 0,81 | | | | | |
| rs8037818 | | | | | | |
| rs74583214 | | | | | | |

## 3.2.3 LD Analysis

Linkage analysis is provided by 3D SNP Annotation tool. Each SNP with LD SNPs are also examined if they have 3D interaction with those SNPs. This analysis provides information about if there is interaction more than LD, there might be more powerful effect on physiology of the obesity risk in the childhood (Quan, C. 2022).

Table 3.8: Linkage Disequilibrium (LD) analysis of childhood related obesity

| **SNP** | **Associated SNP** | **Score** | **R-squared** | **D'** | **Pop.** |
|---|---|---|---|---|---|
| rs7132908 | rs3205718 | 61,1 | 0,98 | 0,99 | EAS |
| rs7132908 | rs3205718 | 61,1 | 0,98 | 1 | SAS |
| rs7132908 | rs3205718 | 61,1 | 0,98 | 0,99 | AFR |
| rs7132908 | rs3205718 | 61,1 | 0,93 | 0,99 | AMR |
| rs7132908 | rs73116325 | 10,39 | 0,92 | 0,97 | EAS |
| rs7132908 | rs12146733 | 10,28 | 0,92 | 0,97 | EAS |
| rs7132908 | rs145103902 | 4,1 | 0,92 | 0,97 | EAS |
| rs7132908 | rs1893492 | 4,03 | 0,92 | 0,97 | EAS |
| rs7132908 | rs3205718 | 61,1 | 0,91 | 0,98 | EUR |

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Cont. of Table 3.8

| | | | | | |
|---|---|---|---|---|---|
| rs7132908 | rs146875448 | 3,98 | 0,86 | 0,94 | EAS |
| rs7132908 | rs7306275 | 9,56 | 0,85 | 0,96 | EUR |
| rs7132908 | rs12367809 | 4,38 | 0,85 | 0,96 | EUR |
| rs7132908 | rs7138803 | 7,34 | 0,84 | 0,96 | EUR |
| rs7132908 | rs112502508 | 4,96 | 0,84 | 0,96 | EUR |
| rs7132908 | rs1893492 | 4,03 | 0,83 | 0,95 | SAS |
| rs7132908 | rs12367809 | 4,38 | 0,82 | 0,92 | SAS |
| rs7132908 | rs145512623 | 3,96 | 0,82 | 0,95 | EAS |
| rs7132908 | rs7306275 | 9,56 | 0,8 | 0,9 | SAS |
| rs7132908 | rs7138803 | 7,34 | 0,8 | 0,92 | SAS |
| rs7132908 | rs112502508 | 4,96 | 0,8 | 0,92 | SAS |

Table 3.4.1 provides information about selected SNPs of childhood obesity related variants and SNPs with LD, Population based D' and $R^2$ results. $R^2 > 0.8$ was selected. The analysis applied all variants. There is also 3D interaction with rs12146733 and rs112502508 variants.

## 3.3 Pathway Analysis

Pathway analysis was applied in Reactome Database (URL7). Pathway description, variation ID, Pathway ID, the system results are expressed in table 3.9 and 3.10 for adulthood and childhood obesity related variants and genes (Griss, J. 2017).

Table: 3.9 Pathway analysis and gene annotation of childhood obesity related variants

| **Pathway ID** | **Description** | **Parent(s)** | **p-Value** | **Genes Involved** | **Variation IDs** |
|---|---|---|---|---|---|
| R-HSA-162582 | Signal Transduction | Signal Transduction | 0.011607 | ACKR1, ADCY3, ARHGAP11A, CCR3, COL4A1, GAS8, GREB1, MATK, MTNR1B, RASGEF1A | rs10830963, rs12075, rs12104221, rs12636651, rs28461806, rs4077678, |

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Cont. of Table 3.9

| | | | | | |
|---|---|---|---|---|---|
| R-HSA-162582 | Signal Transduction | Signal Transduction | 0.011607 | ACKR1, ADCY3, ARHGAP11A, CCR3, COL4A1, GAS8, GREB1, MATK, MTNR1B, RASGEF1A | rs494558, rs73175262, rs74583214, rs8037818 |
| R-HSA-629587 | Highly sodium permeable postsynaptic acetylcholine nicotinic receptors | Neuronal System | 0.011639 | CHRNA3 | rs8040868 |
| R-HSA-73943 | Reversal of alkylation damage by DNA dioxygenases | DNA Repair | 0.011639 | FTO | rs56094641 |
| R-HSA-73942 | DNA Damage Reversal | DNA Repair | 0.013291 | FTO | rs56094641 |
| R-HSA-629597 | Highly calcium permeable nicotinic acetylcholine receptors | Neuronal System | 0.014940 | CHRNA3 | rs8040868 |
| R-HSA-373076 | Class A/1 (Rhodopsin-like receptors) | Signal Transduction | 0.016509 | ACKR1, CCR3, MTNR1B | rs10830963, rs12075, rs12636651 |
| R-HSA-1474151 | Tetrahydrobiopterin (BH4) synthesis, recycling, salvage and regulation | Metabolism | 0.016587 | GCH1 | rs3783637 |
| R-HSA-170660 | Adenylate cyclase activating pathway | Signal Transduction | 0.016587 | ADCY3 | rs4077678 |
| R-HSA-8866904 | Negative regulation of activity of TFAP2 (AP-2) family transcription factors | Gene expression (Transcription) | 0.016587 | TFAP2B | rs2206277 |
| R-HSA-629594 | Highly calcium permeable postsynaptic nicotinic acetylcholine receptors | Neuronal System | 0.018232 | CHRNA3 | rs8040868 |

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Cont. of Table 3.9

| | | | | | |
|---|---|---|---|---|---|
| R-HSA-622323 | Presynaptic nicotinic acetylcholine receptors | Neuronal System | 0.019873 | CHRNA3 | rs8040868 |
| R-HSA-8866907 | Activation of the TFAP2 (AP-2) family of transcription factors | Gene expression (Transcription) | 0.019873 | TFAP2B | rs2206277 |
| R-HSA-1474228 | Degradation of the extracellular matrix | Extracellular matrix organization | 0.022382 | COL4A1, KLKB1 | rs3733402, rs494558 |
| R-HSA-170670 | Adenylate cyclase inhibitory pathway | Signal Transduction; Neuronal System | 0.023149 | ADCY3 | rs4077678 |
| R-HSA-181431 | Acetylcholine binding and downstream events | Neuronal System | 0.023149 | CHRNA3 | rs8040868 |
| R-HSA-622327 | Postsynaptic nicotinic acetylcholine receptors | Neuronal System | 0.023149 | CHRNA3 | rs8040868 |
| R-HSA-2214320 | Anchoring fibril formation | Extracellular matrix organization | 0.024783 | COL4A1 | rs494558 |
| R-HSA-8866910 | TFAP2 (AP-2) family regulates transcription of growth factors and their receptors | Gene expression (Transcription) | 0.024783 | TFAP2B | rs2206277 |
| R-HSA-5358351 | Signaling by Hedgehog | Signal Transduction | 0.025455 | ADCY3, GAS8 | rs4077678, rs74583214 |
| R-HSA-164378 | PKA activation in glucagon signalling | Metabolism | 0.028043 | ADCY3 | rs4077678 |
| R-HSA-418594 | G alpha (i) signalling events | Signal Transduction | 0.028086 | ADCY3, CCR3, MTNR1B | rs10830963, rs12636651, rs4077678 |
| R-HSA-163615 | PKA activation | Signal Transduction | 0.029669 | ADCY3 | rs4077678 |
| R-HSA-2243919 | Crosslinking of collagen fibrils | Extracellular matrix organization | 0.029669 | COL4A1 | rs494558 |
| R-HSA-5635838 | Activation of SMO | Signal Transduction | 0.029669 | GAS8 | rs74583214 |
| R-HSA-3000480 | Scavenging by Class A Receptors | Vesicle-mediated transport | 0.031293 | COL4A1 | rs494558 |

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Cont. of Table 3.9

| | | | | | |
|---|---|---|---|---|---|
| R-HSA-8978934 | Metabolism of cofactors | Metabolism | 0.031293 | GCH1 | rs3783637 |
| R-HSA-111931 | PKA-mediated phosphorylation of CREB | Signal Transduction | 0.032914 | ADCY3 | rs4077678 |
| R-HSA-3232118 | SUMOylation of transcription factors | Metabolism of proteins | 0.032914 | TFAP2B | rs2206277 |
| R-HSA-140837 | Intrinsic Pathway of Fibrin Clot Formation | Hemostasis | 0.037762 | KLKB1 | rs3733402 |
| R-HSA-500792 | GPCR ligand binding | Signal Transduction | 0.039572 | ACKR1, CCR3, MTNR1B | rs10830963, rs12075, rs12636651 |
| R-HSA-375276 | Peptide ligand-binding receptors | Signal Transduction | 0.041995 | ACKR1, CCR3 | rs12075, rs12636651 |
| R-HSA-264876 | Insulin processing | Metabolism of proteins | 0.044191 | PCSK2 | rs6044834 |
| R-HSA-112314 | Neurotransmitter receptors and postsynaptic signal transmission | Neuronal System | 0.045129 | ADCY3, CHRNA3 | rs4077678, rs8040868 |
| R-HSA-8863795 | Downregulation of ERBB2 signaling | Signal Transduction | 0.047389 | MATK | rs12104221 |
| R-HSA-3000157 | Laminin interactions | Extracellular matrix organization | 0.048985 | COL4A1 | rs494558 |

Table: 3.10 Pathway analysis and gene annotation of adulthood obesity related variants

| **Pathway ID** | **Description** | **Parent(s)** | **p-Value** | **Genes Involved** | **Variation IDs** |
|---|---|---|---|---|---|
| R-HSA-156580 | Phase II - Conjugation of compounds | Metabolism | 0.000000 | UGT1A1, UGT1A10, UGT1A3, UGT1A4, UGT1A5, UGT1A6, UGT1A7, UGT1A8, UGT1A9 | rs4148325 |

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Cont. of Table 3.10

| | | | | | |
|---|---|---|---|---|---|
| R-HSA-156588 | Glucuronidation | Metabolism | 0.000000 | UGT1A1, UGT1A10, UGT1A3, UGT1A4, UGT1A5, UGT1A6, UGT1A7, UGT1A8, UGT1A9 | rs4148325 |
| R-HSA-211859 | Biological oxidations | Metabolism | 0.000003 | UGT1A1, UGT1A10, UGT1A3, UGT1A4, UGT1A5, UGT1A6, UGT1A7, UGT1A8, UGT1A9 | rs4148325 |
| R-HSA-170670 | Adenylate cyclase inhibitory pathway | Signal Transduction;Neuronal System | 0.000057 | ADCY3, ADCY9, GNAI3 | rs1541984, rs17024258, rs2531995 |
| R-HSA-418597 | G alpha (z) signalling events | Signal Transduction | 0.000141 | ADCY3, ADCY9, GNAI3, PRKCH | rs1541984, rs17024258, rs1957894, rs2531995 |
| R-HSA-112043 | PLC beta mediated events | Signal Transduction | 0.000207 | ADCY3, ADCY9, GNAI3, GNAT2 | rs1541984, rs17024258, rs2531995 |
| R-HSA-112040 | G-protein mediated events | Signal Transduction | 0.000223 | ADCY3, ADCY9, GNAI3, GNAT2 | rs1541984, rs17024258, rs2531995 |

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Cont. of Table 3.10

| | | | | | |
|---|---|---|---|---|---|
| R-HSA-166658 | Complement cascade | Immune System | 0.000417 | C7, CFB, CFH, CPN1, FCN2 | rs11599750, rs1329428, rs3805221, rs541862, rs7851696 |
| R-HSA-170660 | Adenylate cyclase activating pathway | Signal Transduction | 0.001333 | ADCY3, ADCY9 | rs1541984, rs2531995 |
| R-HSA-111885 | Opioid Signalling | Signal Transduction | 0.001618 | ADCY3, ADCY9, GNAI3, GNAT2 | rs1541984, rs17024258, rs2531995 |
| R-HSA-2586552 | Signaling by Leptin | Signal Transduction | 0.001624 | LEPR, SH2B1 | rs11208659, rs7498665 |
| R-HSA-977444 | GABA B receptor activation | Neuronal System | 0.001729 | ADCY3, ADCY9, GNAI3 | rs1541984, rs17024258, rs2531995 |
| R-HSA-991365 | Activation of GABAB receptors | Neuronal System | 0.001729 | ADCY3, ADCY9, GNAI3 | rs1541984, rs17024258, rs2531995 |
| R-HSA-977606 | Regulation of Complement cascade | Immune System | 0.002548 | C7, CFB, CFH, CPN1 | rs11599750, rs1329428, rs3805221, rs541862 |
| R-HSA-109582 | Hemostasis | Hemostasis | 0.003836 | ATP2A1, DGKG, ECM1, GNAI3, KCNMA1, PRKCH, PRTN3, SERPINA4, SERPINA5, SH2B1 | rs13294, rs1516725, rs17024258, rs1957894, rs2074639, rs2116830, rs5510, rs7189927, rs7498665, rs9816226 |
| R-HSA-164378 | PKA activation in glucagon signalling | Metabolism | 0.003930 | ADCY3, ADCY9 | rs1541984, rs2531995 |
| R-HSA-163615 | PKA activation | Signal Transduction | 0.004405 | ADCY3, ADCY9 | rs1541984, rs2531995 |

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| | | | | | |
|---|---|---|---|---|---|
| R-HSA-977443 | GABA receptor activation | Neuronal System | 0.004484 | ADCY3, ADCY9, GNAI3 | rs1541984, rs17024258, rs2531995 |
| R-HSA-111931 | PKA-mediated phosphorylation of CREB | Signal Transduction | 0.005432 | ADCY3, ADCY9 | rs1541984, rs2531995 |
| R-HSA-5579002 | Defective UGT1A1 causes hyperbilirubinemia | Disease | 0.005568 | UGT1A1 | rs4148325 |
| R-HSA-5579016 | Defective UGT1A4 causes hyperbilirubinemia | Disease | 0.005568 | UGT1A4 | rs4148325 |
| R-HSA-5619037 | Defective SLC35A1 causes congenital disorder of glycosylation 2F (CDG2F) | Disease | 0.005568 | SLC35A1 | rs2268992 |
| R-HSA-5663020 | Defective SLC35A1 causes congenital disorder of glycosylation 2F (CDG2F) | Disease | 0.005568 | SLC35A1 | rs2268992 |
| R-HSA-9660821 | ADORA2B mediated anti-inflammatory cytokines production | Disease | 0.006344 | ADCY3, ADCY9, GIPR, GNAI3 | rs10423928, rs1541984, rs17024258, rs1800437, rs2531995 |
| R-HSA-140875 | Common Pathway of Fibrin Clot Formation | Hemostasis | 0.006557 | PRTN3, SERPINA5 | rs2074639, rs5510 |
| R-HSA-449836 | Other interleukin signaling | Immune System | 0.007779 | IL16, PRTN3 | rs2074639, rs4778636 |
| R-HSA-114508 | Effects of PIP2 hydrolysis | Signal Transduction Hemostasis | 0.009787 | DGKG, PRKCH | rs1516725, rs1957894, rs9816226 |
| R-HSA-202040 | G-protein activation | Signal Transduction | 0.010503 | GNAI3, GNAT2 | rs17024258 |

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| | | | | | |
|---|---|---|---|---|---|
| R-HSA-198765 | Signalling to ERK5 | Signal Transduction | 0.011106 | MAP2K5 | rs8028313 |
| R-HSA-9024909 | BDNF activates NTRK2 (TRKB) signaling | Signal Transduction | 0.011106 | BDNF | rs16917237, rs2030323 |
| R-HSA-163359 | Glucagon signaling in metabolic regulation | Metabolism | 0.014412 | ADCY3, ADCY9 | rs1541984, rs2531995 |
| R-HSA-76002 | Platelet activation, signaling and aggregation | Hemostasis | 0.014836 | DGKG, ECM1, GNAI3, PRKCH, SERPINA4 | rs13294, rs1516725, rs17024258, rs1957894, rs5510, rs9816226 |
| R-HSA-111933 | Calmodulin induced events | Signal Transduction | 0.016125 | ADCY3, ADCY9 | rs1541984, rs2531995 |
| R-HSA-111997 | CaM pathway | Signal Transduction | 0.016125 | ADCY3, ADCY9 | rs1541984, rs2531995 |
| R-HSA-9014843 | Interleukin-33 signaling | Immune System | 0.016614 | IL1RAP | rs6444444 |
| R-HSA-5579029 | Metabolic disorders of biological oxidation enzymes | Disease | 0.017014 | UGT1A1, UGT1A4 | rs4148325 |
| R-HSA-111996 | Ca-dependent events | Signal Transduction | 0.017922 | ADCY3, ADCY9 | rs1541984, rs2531995 |
| R-HSA-140877 | Formation of Fibrin Clot (Clotting Cascade) | Hemostasis | 0.019799 | PRTN3, SERPINA5 | rs2074639, rs5510 |
| R-HSA-1489509 | DAG and IP3 signaling | Signal Transduction | 0.021756 | ADCY3, ADCY9 | rs1541984, rs2531995 |
| R-HSA-9022538 | Loss of MECP2 binding ability to 5mC-DNA | Disease | 0.022091 | BDNF | rs16917237, rs2030323 |
| R-HSA-9026527 | Activated NTRK2 signals through PLCG1 | Signal Transduction | 0.022091 | BDNF | rs16917237, rs2030323 |

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| | | | | | |
|---|---|---|---|---|---|
| R-HSA-6814122 | Cooperation of PDCL (PhLP1) and TRiC/CCT in G-protein beta folding | Metabolism of proteins | 0.022763 | GNAI3, GNAT2 | rs17024258 |
| R-HSA-432040 | Vasopressin regulates renal water homeostasis via Aquaporins | Transport of small molecules | 0.023789 | ADCY3, ADCY9 | rs1541984, rs2531995 |
| R-HSA-418594 | G alpha (i) signalling events | Signal Transduction | 0.024359 | ADCY3, ADCY9, CCL16, CCR3, GNAI3, GNAT2 | rs11080369, rs1541984, rs17024258, rs2531995, rs3136673 |
| R-HSA-112316 | Neuronal System | Neuronal System | 0.025955 | ADCY3, ADCY9, GNAI3, IL1RAP, KCNMA1, NRXN3 | rs11624704, rs1541984, rs17024258, rs2116830, rs2370983, rs2531995, rs6444444, rs7141420 |
| R-HSA-173736 | Alternative complement activation | Immune System | 0.027539 | CFB | rs541862 |
| R-HSA-2855086 | Ficolins bind to repetitive carbohydrate structures on the target cell surface | Immune System | 0.027539 | FCN2 | rs7851696 |
| R-HSA-9032759 | NTRK2 activates RAC1 | Signal Transduction | 0.027539 | BDNF | rs16917237, rs2030323 |
| R-HSA-8939245 | RUNX1 regulates transcription of genes involved in BCR signaling | Gene expression (Transcription) | 0.032957 | PAX5 | rs16933812 |

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| | | | | | |
|---|---|---|---|---|---|
| R-HSA-9032845 | Activated NTRK2 signals through CDK5 | Signal Transduction | 0.032957 | BDNF | rs16917237, rs2030323 |
| R-HSA-445717 | Aquaporin-mediated transport | Transport of small molecules | 0.033839 | ADCY3, ADCY9 | rs1541984, rs2531995 |
| R-HSA-9662851 | Anti-inflammatory response favouring Leishmania parasite infection | Disease | 0.035368 | ADCY3, ADCY9, GIPR, GNAI3 | rs10423928, rs1541984, rs17024258, rs1800437, rs2531995 |
| R-HSA-9664433 | Leishmania parasite growth and survival | Disease | 0.035368 | ADCY3, ADCY9, GIPR, GNAI3 | rs10423928, rs1541984, rs17024258, rs1800437, rs2531995 |
| R-HSA-174577 | Activation of C3 and C5 | Immune System | 0.038344 | CFB | rs541862 |
| R-HSA-73943 | Reversal of alkylation damage by DNA dioxygenases | DNA Repair | 0.038344 | FTO | rs1421085, rs1558902, rs17817449, rs7185735, rs8043757, rs8050136, rs9941349 |
| R-HSA-9014826 | Interleukin-36 pathway | Immune System | 0.038344 | IL1RAP | rs6444444 |
| R-HSA-9028335 | Activated NTRK2 signals through PI3K | Signal Transduction | 0.038344 | BDNF | rs16917237, rs2030323 |
| R-HSA-9032500 | Activated NTRK2 signals through FYN | Signal Transduction | 0.038344 | BDNF | rs16917237, rs2030323 |
| R-HSA-380108 | Chemokine receptors bind chemokines | Signal Transduction | 0.040018 | CCL16, CCR3 | rs11080369, rs3136673 |
| R-HSA-166662 | Lectin pathway of complement activation | Immune System | 0.043703 | FCN2 | rs7851696 |

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| | | | | | |
|---|---|---|---|---|---|
| R-HSA-166665 | Terminal pathway of complement | Immune System | 0.043703 | C7 | rs3805221 |
| R-HSA-73942 | DNA Damage Reversal | DNA Repair | 0.043703 | FTO | rs1421085, rs1558902, rs17817449, rs7185735, rs8043757, rs8050136, rs9941349 |
| R-HSA-9022702 | MECP2 regulates transcription of neuronal ligands | Gene expression (Transcription) | 0.043703 | BDNF | rs16917237, rs2030323 |
| R-HSA-1296052 | Ca2+ activated K+ channels | Neuronal System | 0.049032 | KCNMA1 | rs2116830 |
| R-HSA-727802 | Transport of nucleotide sugars | Transport of small molecules | 0.049032 | SLC35A1 | rs2268992 |
| R-HSA-9026519 | Activated NTRK2 signals through RAS | Signal Transduction | 0.049032 | BDNF | rs16917237, rs2030323 |
| R-HSA-9623433 | NR1H2 & NR1H3 regulate gene expression to control bile acid homeostasis | Signal Transduction | 0.049032 | UGT1A3 | rs4148325 |

Table 3.9 and 3.10 shows pathway analysis of both childhood and adulthood related gene annotations and pathways of proteins encoded by genes. For both analysis p – value < 0.05 included in both tables (Griss, J. 2017).

Figure 3.3 and Figure 3.4 are shown obesity related gene encoding protein pathways. In figure 3.3 childhood obesity related pathways are mostly found in signal transduction pathways. In Figure 3.4 adulthood obesity related pathways are found in metabolism, homeostasis, signaling pathway. Some of the pathways are related with immune system. Small partition of adulthood related pathways are neurologic pathways (Griss, J. 2017).

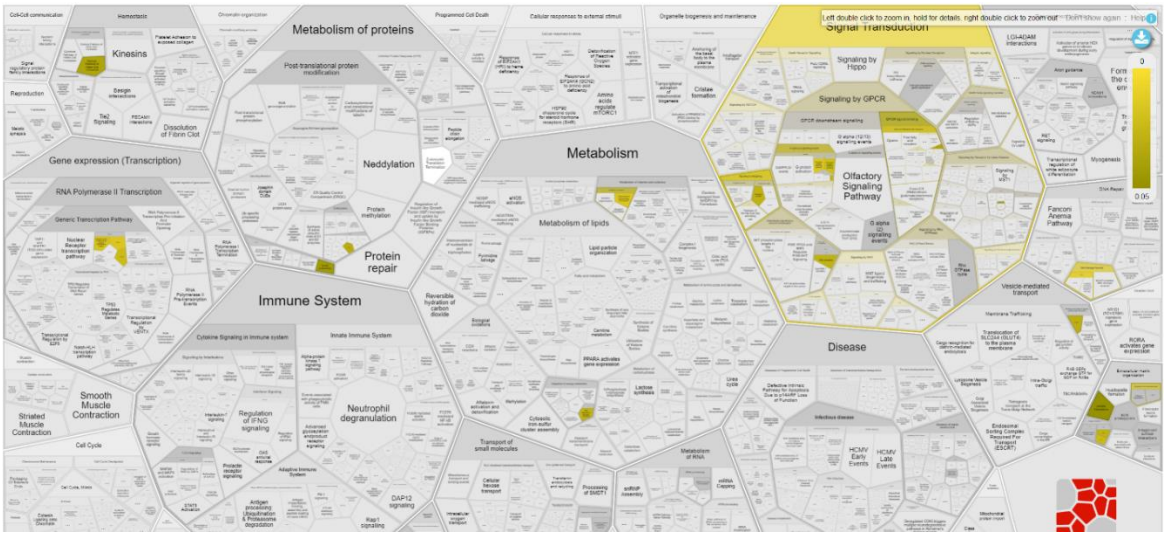


Figure 3.3 Childhood obesity related genes pathway analysis

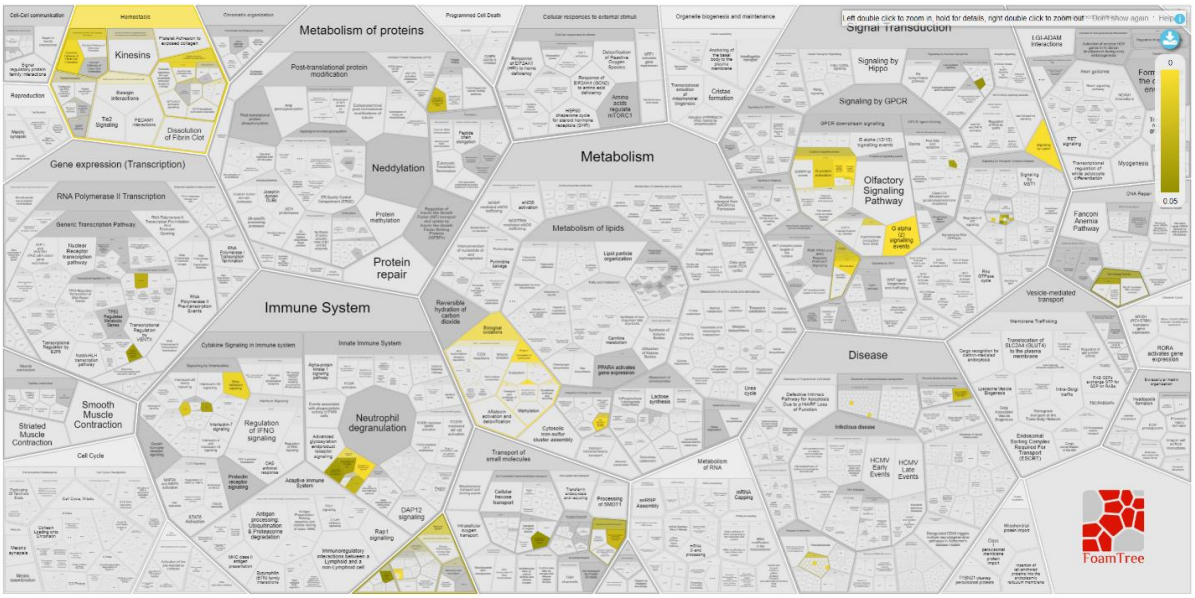


Figure 3.4 Adulthood obesity related genes pathway analysis

Figures represents full childhood and adulthood related pathways without any discrimination.

## 3.4 Protein- Protein Interaction Network Analysis

Protein – protein interaction network analysis provides additional information if there is overlap, protein interaction or co expression of proteins those are related with childhood and adulthood obesity. The analysis also inform interaction within the group of SNPs.

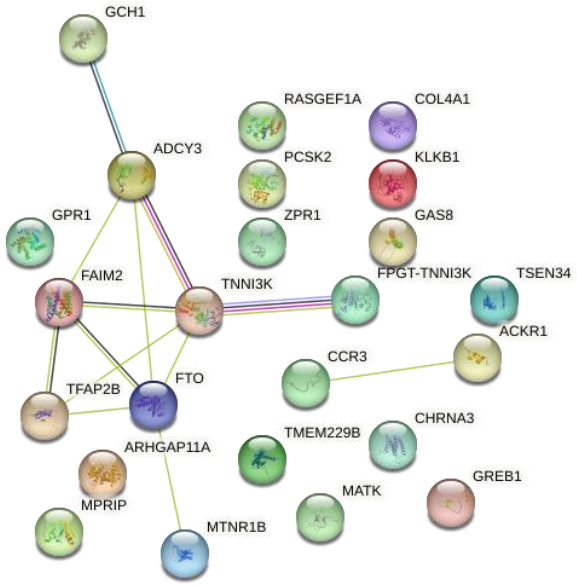


Figure 3.5 Childhood obesity related proteins network analysis

In Figure 3.5 within childhood obesity related proteins, *GCH1, ADCY3, FAIM2, TNNIK3, TFAP2B, FTO, ARHGAP11A, FPGT-TNNI3K* are in interaction. Expanding candidate gene variant-related studies and mapping the relevant protein interactions are thought to be important for the next step in order to establish a childhood obesity polygenic risk score calculation panel. It is important to include not only childhood but also adult obesity-related variants in similar pathways and interactions (Szklarczyk, D. 2023).

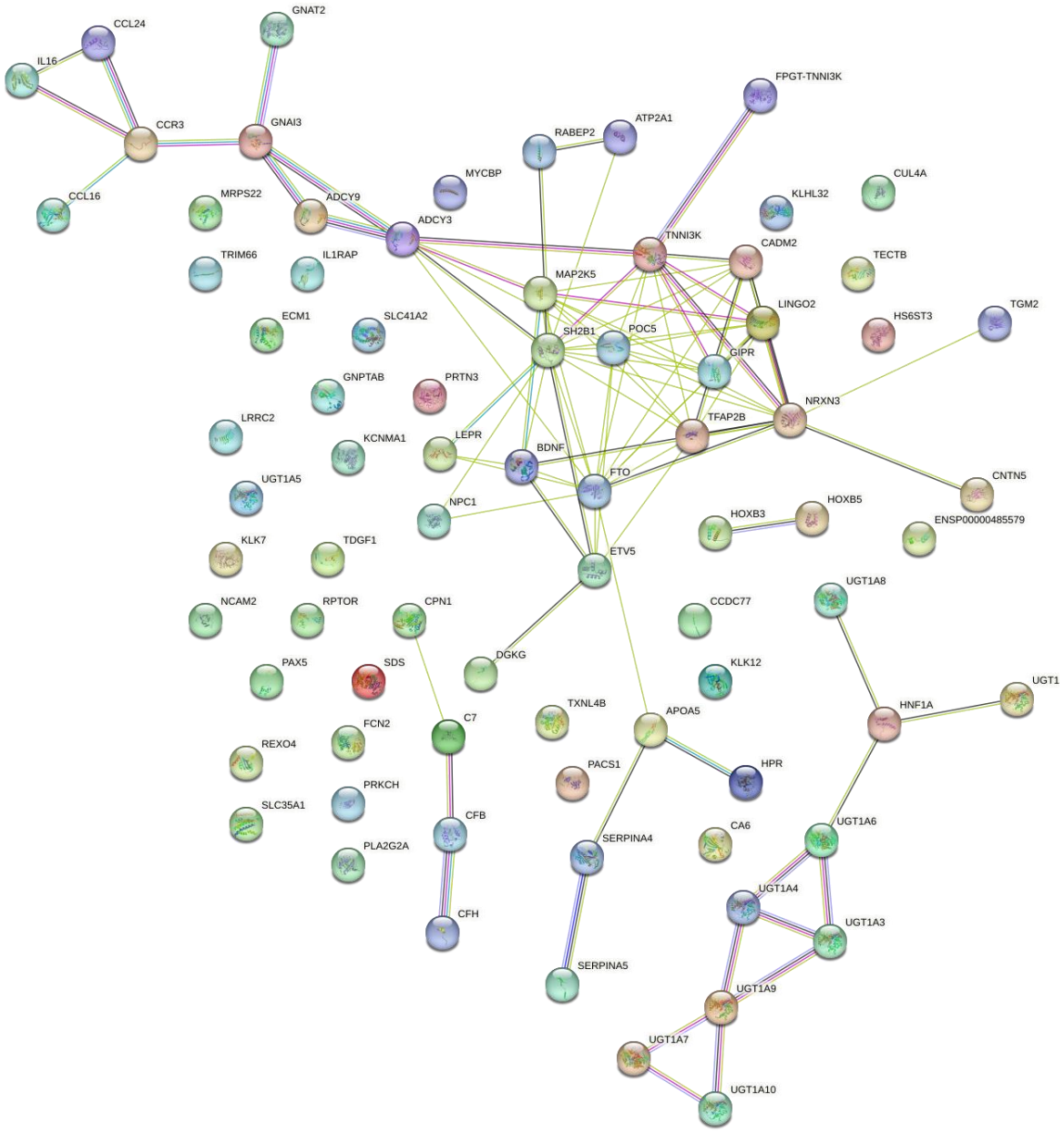


Figure 3.6 Adulthood obesity related proteins network analysis

In Figure 3.6, *MAP2K*, *TFAP2*, *NRXN3*, *FTO*, *BDNF*, *ETV5*, *SH2B1*, *MAP2K5*, *RABEP2*, *FPGT-TNNIK3*, *POC5*, *GIPR*, *LINGO2*, *CADM2*, *ADCY3*, *ADCY9*, *GNAI3*, *CCR3*, *IL16*, *RABEP2*, *ATP2A1*, *LEPR NPC1* proteins have more interaction than the others.

## 3.5 Polygenic Risk Score Calculation

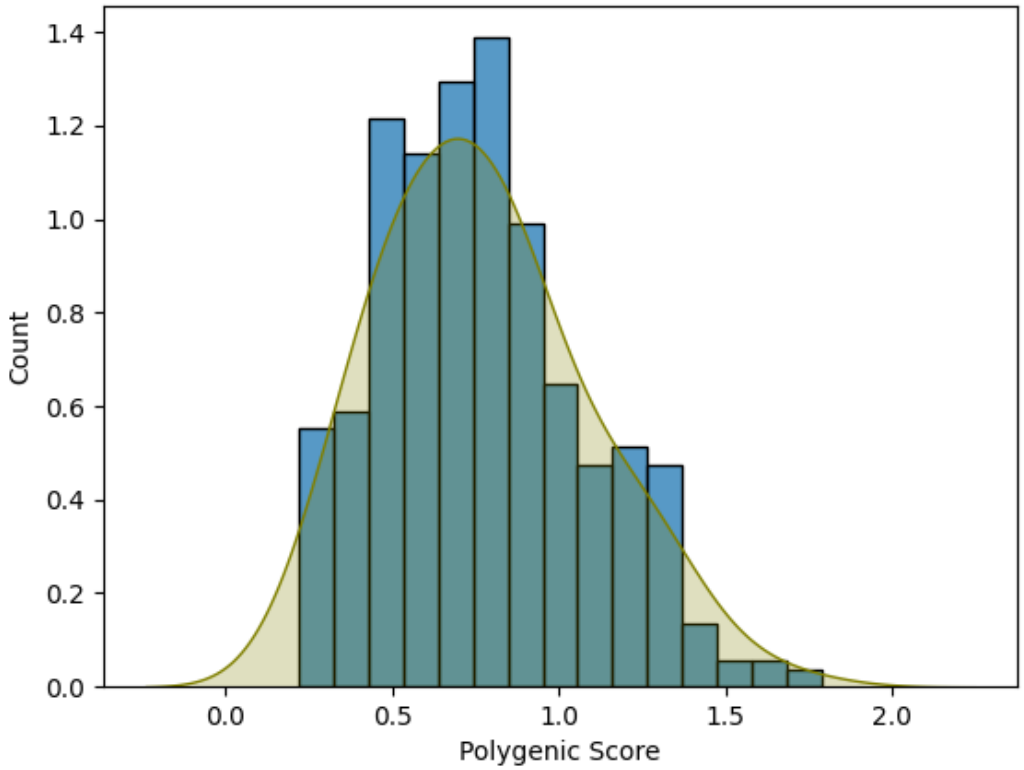


Figure 3.7 Polygenic Risk Score calculation results from childhood obesity related variants

33 variants predominantly Hispanic population were used to calculate the polygenic risk score. beta value is taken as estimated effect size. 1000 genome data were taken as QC (quality control) data set in the data set. in each calculation, the presence of the relevant allele was multiplied by the beta value and added. thus, a basic polygenic risk score calculation was performed (The 1000 Genomes Project Consortium, 2015).

# CHAPTER 4

# DISCUSSION

The polygenic effect of obesity continues to be investigated. The aim of this thesis is to investigate the polygenic effects of childhood obesity and adulthood obesity, to reveal the differences, to examine the interaction between the two groups in terms of genes and pathways, protein-protein interaction network, to determine the total effect of the polygenic risk score and the variants that affect the childhood, and to determine the genetic risk score panel.

First of all, variants those affect childhood and adulthood obesity are listed. From GWAS Catalog, all populations were included throughout this investigation. Variants those have p value $p<1 \times 10^{-6}$ are listed but for the analysis only $p<1 \times 10^{-8}$ are included as indicated in the literature. When compared the childhood and adulthood obesity related variants, only 1 variant found overlap in the rs2206277 *TFAP2B* gene region. This variant is located in the intronic protein-coding gene region of the 6th chromosome. The associated variant was also revealed in 3D SNP analyzes of the *TFAP2D* gene. The *TFAP2* family of proteins is responsible for the transcription of growth factor. It has also been discovered in protein metabolism pathway.

Secondly, SNPs are shown in autosomal chromosomes. As indicated in results, there is no aggregation on specific chromosomes.

With SNP annotation, regions of SNPs, genes, genes located upstream and downstream were expressed. Long noncoding RNA, snRNA, miscRNA coding gene regions were found in almost all of the variants that are not located in the gene region. It can be evaluated as the output of research whether the RNA-coding gene regions located in the close regions of these variants related to childhood and adulthood obesity play a regulatory role.

Similarly, when three-dimensional annotation was performed, it was revealed that some of the variants in LD interacted in three-dimensional structure. As a result, evaluating variants not only on the genome but also with other variants with which they interact may help us to understand more comprehensively.

In the LD analysis and 3D SNP interaction analysis, it was determined that the rs56094641 variant in the *FTO* gene associated with childhood obesity interacts with the rs1558902, rs1121980, rs1421085, rs17817449, rs8043757 variants. These interacting variants are among the variants that have a significant impact on adult obesity. *FTO* is one of the most associative gene both found in adulthood and childhood related variants. As a result, even if variants in the *FTO* gene are not found to be related, calculations can be performed by including them for both groups risk.

In the pathway analysis, proteins associated with childhood obesity are particularly involved in signal transduction, while proteins associated with adult obesity are involved in both the signal pathway, metabolism and neural system (URL7). Considering the stages of development, when childhood obesity is evaluated, it may be possible that a certain number of functions are fulfilled and it may emerge as childhood obesity.

Obesity in adulthood, especially proteins that affect metabolism and the neural system were found to be more frequently associated. *BDNF* is one of the candidate genes and it is stated in many studies that it determines both mood and eating habits. In order to understand these studies in detail, the results of obesity groups from childhood and continuing into adulthood should be discussed.

In protein protein-protein interaction network analysis, the proteins that encode by *FTO, ADCY3, TNNI3K, FPGT-TNNI3K* genes are among the proteins that affect both childhood and adult obesity. Of the three genes, *ADCY3* is involved in signal transduction, energy activation and neural signal transduction. Particularly common in adulthood and childhood obesity suggests that this gene may have an important role in the emergence of obesity and other metabolic diseases. *TINNI3K*, which is involved in signal transduction, has been associated with overweight in more than one study. Similarly, it has been associated with cardiac physiology (URL8).

Finally, when the polygenic risk score was evaluated, the presence of variants predominantly from the Hispanic population did not significantly change the distribution.

This is because a limited number of variants provide results in the searched criteria. In this study, the fact that the population structure and the entire structure of the data obtained are not fully determined limits the use of the polygenic risk score. However, in the basic calculation with a small group of variants and beta value only, a total score of close to 2 was calculated in a small group. Accordingly, when calculating the polygenic risk score, especially when the risk of childhood obesity is evaluated, calculations can be made from data with a similar population structure.

As a result, in the data obtained, variants, genes, proteins encoded by these genes and pathways that affect childhood obesity and adult obesity are in a very small intersection. There is an interaction between the genes that affect both groups and contribute to a certain part of polygenic obesity and the variants in these genes.

# CHAPTER 5

# CONCLUSION

In this thesis, variant, gene, protein, pathway and polygenic risk calculations were performed by comparing childhood obesity with some adult obesity. Calculation of polygenic risk score remained at the basic and limited level due to the small size of the data set. In future studies, there should be more extensive datasets to carry out more comprehensive studies on individuals who experience obesity from childhood to adulthood.

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# APPENDIX A

In Appendix A, partially childhood related obesity variants are listed.

| Variant and risk allele | P-value | P-value annotation | RAF | OR | Beta | CI | Mapped gene | Reported trait | Trait(s) | Study accession | | Population |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs12075 | 1 x 10-21 | (MCP1 ) | 436 | - | 0.1 pg/mL increase | [NR] | ACKR1, CADM3-AS1 | Obesity-related traits | CCL2 measurement | GCST001762 | 2653427:04:00 | Hispanic |
| rs1443438 | 1 x 10-9 | (TSH ) | 253 | - | 0.04 µIU/mL increase | [NR] | PTCSC2 | Obesity-related traits | thyroid stimulating hormone measurement | GCST001762 | 1629804:46:00 | Hispanic |
| rs12636651 | 7 x 10-9 | (MCP1 ) | 403 | - | 0.05 pg/mL increase | [NR] | CCR3 | Obesity-related traits | CCL2 measurement | GCST001762 | 770684:40:00 | Hispanic |
| rs79509430 | 2 x 10-8 | (MCP1 ) | 68 | - | 0.06 pg/mL increase | [NR] | WHRN | Obesity-related traits | CCL2 measurement | GCST001762 | 2221073:22:00 | Hispanic |
| rs657152 | 2 x 10-8 | (IL6 ) | 254 | - | 0.04 pg/mL increase | [NR] | ABO | Obesity-related traits | interleukin-6 measurement | GCST001762 | 1907986:06:00 | Hispanic |
| rs7595 | 3 x 10-8 | (Height change ) | 389 | - | 0.05 cm/y increase | [NR] | TSEN34 | Obesity-related traits | body height | GCST001762 | 1946458:25:00 | Hispanic |
| rs3741298 | 3 x 10-8 | (TG ) | 0.48 | - | 0.04 mg/dL increase | [NR] | ZPR1 | Obesity-related traits | triglyceride measurement | GCST001762 | 903239:24:00 | Hispanic |
| rs12104221 | 3 x 10-8 | (Total energy expenditure adj for weight ) | 381 | - | 0.05 kcal/d increase | [NR] | MATK | Obesity-related traits | energy expenditure | GCST001762 | 63304:02:00 | Hispanic |
| rs6025590 | 4 x 10-8 | (Sedentary&light activity ) | 308 | - | 0.04 min/d increase | [NR] | CTCFL, HMGB1P1 | Obesity-related traits | physical activity | GCST001762 | 958277:29:00 | Hispanic |
| rs10830963 | 4 x 10-8 | (GLU ) | 205 | - | 0.05 mg/dL increase | [NR] | MTNR1B | Obesity-related traits | fasting blood glucose measurement | GCST001762 | 1549603:24:00 | Hispanic |
| rs8037818 | 5 x 10-8 | (Sleep duration ) | 181 | - | 0.04 min/d increase | [NR] | ARHGAP11A | Obesity-related traits | sleep measurement | GCST001762 | 543936:15:00 | Hispanic |
| rs494558 | 5 x 10-8 | (Weight z-score change ) | 78 | - | 0.05 SD/y increase | [NR] | COL4A1 | Obesity-related traits | body weight | GCST001762 | 268534:33:00 | Hispanic |
| rs28461806 | 5 x 10-8 | (MCP1 ) | 49 | - | 0.05 pg/mL increase | [NR] | RASGEF1A | Obesity-related traits | CCL2 measurement | GCST001762 | 1837959:55:00 | Hispanic |
| rs2823615 | 5 x 10-8 | (Sleep RQ) | 178 | - | 0.04 unit increase | [NR] | MIR99AHG | Obesity-related traits | respiratory quotient | GCST001762 | 1124560:06:00 | Hispanic |
| rs17104363 | 5 x 10-8 | (Dinner intake, adj EER ) | 0.05 | - | 0.04 kcal increase | [NR] | TMEM229B | Obesity-related traits | energy intake | GCST001762 | 721015:06:00 | Hispanic |
| rs8040868 | 6 x 10-8 | (Sleep energy expenditure adj weight ) | 239 | - | 0.05 kcal/d increase | [NR] | CHRNA3 | Obesity-related traits | energy expenditure | GCST001762 | 1310328:59:00 | Hispanic |
| rs3783637 | 6 x 10-8 | (Urinary free dopamine: creatinine) | 121 | - | 0.05 unit increase | [NR] | GCH1 | Obesity-related traits | urinary metabolite measurement | GCST001762 | 914704:00:00 | Hispanic |
| rs73175262 | 7 x 10-8 | (MCP1 ) | 53 | - | 0.05 pg/mL increase | [NR] | GREB1 | Obesity-related traits | CCL2 measurement | GCST001762 | 193640:25:00 | Hispanic |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs61744862 | 7 x 10-8 | (IGFBP-3 ) | 41 | - | 0.04 ng/mL increase | [NR] | MPRIP | Obesity-related traits | IGFBP-3 measurement | GCST001762 | 286098:08:00 | Hispanic |
| rs6044834 | 8 x 10-8 | (Total antioxidants ) | 69 | - | 0.04 mM increase | [NR] | PCSK2 | Obesity-related traits | antioxidant measurement | GCST001762 | 346573:34:00 | Hispanic |
| rs16933006 | 8 x 10-8 | (Light activity ) | 0.11 | - | 0.04 min/d increase | [NR] | TTC39B, RPL7P33 | Obesity-related traits | physical activity | GCST001762 | 351807:59:00 | Hispanic |
| rs11974269 | 8 x 10-8 | (Urinary creatinine ) | 128 | - | 0.05 mmol/d increase | [NR] | LINC01162 | Obesity-related traits | urinary metabolite measurement | GCST001762 | 255607:36:00 | Hispanic |
| rs10131141 | 8 x 10-8 | (Urinary nitrogen ) | 0.28 | - | 0.04 g/d increase | [NR] | RNASE1, RNASE6 | Obesity-related traits | urinary nitrogen measurement | GCST001762 | 290950:28:00 | Hispanic |
| rs3733402 | 9 x 10-8 | (IGF1 free ) | 337 | - | 0.04 ng/mL increase | [NR] | KLKB1 | Obesity-related traits | IGF-1 measurement | GCST001762 | 3103952:00:00 | Hispanic |
| rs6061910 | 1 x 10-7 | (IGFBP-3 ) | 63 | - | 0.04 ng/mL increase | [NR] | CDH4 | Obesity-related traits | IGFBP-3 measurement | GCST001762 | 1031911:26:00 | Hispanic |
| rs589756 | 1 x 10-7 | (Lean body mass ) | 129 | - | 0.04 kg increase | [NR] | MOXD1 | Obesity-related traits | lean body mass | GCST001762 | 1438931:20:00 | Hispanic |
| rs589756 | 1 x 10-7 | (Fat free mass ) | 129 | - | 0.04 kg increase | [NR] | MOXD1 | Obesity-related traits | body composition measurement | GCST001762 | 2205372:18:00 | Hispanic |
| rs58632700 | 1 x 10-7 | (Free T3 ) | 77 | - | 0.05 pg/mL increase | [NR] | SLC27A5, ZNF446 | Obesity-related traits | hormone measurement | GCST001762 | 2205372:18:00 | Hispanic |
| rs4083242 | 1 x 10-7 | (Sedentary&light activity ) | 336 | - | 0.03 min/d increase | [NR] | LINC00917 | Obesity-related traits | physical activity | GCST001762 | 974696:14:00 | Hispanic |
| rs11863065 | 1 x 10-7 | (Hip circumference ) | 0.03 | - | 0.04 cm increase | [NR] | - | Obesity-related traits | hip circumference | GCST001762 | 1032238:44:00 | Hispanic |
| rs1056513 | 1 x 10-7 | (Weight ) | 495 | - | 0.03 kg increase | [NR] | PATJ | Obesity-related traits | body weight | GCST001762 | 1371569:20:00 | Hispanic |
| rs7654585 | 2 x 10-7 | (WC change ) | 374 | - | 0.04 cm/y increase | [NR] | SMIM20 | Obesity-related traits | waist circumference | GCST001762 | 1031911:26:00 | Hispanic |
| rs7650267 | 2 x 10-7 | (Eotaxin ) | 93 | - | 0.04 pg/mL increase | [NR] | ANO10 | Obesity-related traits | CCL11 measurement | GCST001762 | 1031911:26:00 | Hispanic |
| rs4356975 | 2 x 10-7 | (Gestational age ) | 295 | - | 0.07 wk increase | [NR] | UGT2B7 | Obesity-related traits | gestational age | GCST001762 | 432356:09:00 | Hispanic |
| rs3919627 | 2 x 10-7 | (Eotaxin ) | 353 | - | 0.03 pg/mL increase | [NR] | KRBOX1, CYP8B1, ACKR2 | Obesity-related traits | CCL11 measurement | GCST001762 | 714464:08:00 | Hispanic |
| rs3864639 | 2 x 10-7 | (Urinary nitrogen ) | 88 | - | 0.05 g/d increase | [NR] | FAM185BP | Obesity-related traits | urinary nitrogen measurement | GCST001762 | 1151783:05:00 | Hispanic |
| rs333960 | 2 x 10-7 | (QUICKl) | 144 | - | 0.04 unit increase | [NR] | LINC01768, CSF1 | Obesity-related traits | insulin sensitivity measurement | GCST001762 | 1396724:30:00 | Hispanic |
| rs1913185 | 2 x 10-7 | (NEFA ) | 249 | - | 0.04 mmol/L increase | [NR] | PLSCR4, PLOD2 | Obesity-related traits | fatty acid measurement | GCST001762 | 2436180:50:00 | Hispanic |
| rs16839626 | 2 x 10-7 | (Energy storage ) | 60 | - | 0.05 kcal/d increase | [NR] | NBEAL1 | Obesity-related traits | body composition measurement | GCST001762 | 2011777:44:00 | Hispanic |
| rs16839626 | 2 x 10-7 | (Fat mass deposition ) | 60 | - | 0.05 kcal/d increase | [NR] | NBEAL1 | Obesity-related traits | body composition measurement | GCST001762 | 1831615:18:00 | Hispanic |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs13077101 | 2 x 10-7 | (AST/ALT) | 177 | - | 0.03 unit increase | [NR] | RABL3 | Obesity-related traits | aspartate aminotransferase measurement, serum alanine aminotransferase measurement | GCST001762 | 723776:23:00 | Hispanic |
| rs11116045 | 2 x 10-7 | (Eotaxin ) | 269 | - | 0.03 pg/mL increase | [NR] | - | Obesity-related traits | CCL11 measurement | GCST001762 | 1285161:34:00 | Hispanic |
| rs1056513 | 2 x 10-7 | (Trunk fat mass ) | 495 | - | 0.04 kg increase | [NR] | PATJ | Obesity-related traits | body composition measurement | GCST001762 | 3387085:27:00 | Hispanic |
| rs1056513 | 2 x 10-7 | (Fat mass ) | 495 | - | 0.04 kg increase | [NR] | PATJ | Obesity-related traits | body composition measurement | GCST001762 | 3387085:27:00 | Hispanic |
| rs7825271 | 3 x 10-7 | (AST ) | 251 | - | 0.04 U/L increase | [NR] | C8orf34 | Obesity-related traits | aspartate aminotransferase measurement | GCST001762 | 1031911:26:00 | Hispanic |
| rs7822058 | 3 x 10-7 | (Leptin ) | 76 | - | 0.04 ng/mL increase | [NR] | RB1CC1 | Obesity-related traits | leptin measurement | GCST001762 | 1031911:26:00 | Hispanic |
| rs7814403 | 3 x 10-7 | (Diet carbohydrate ) | 462 | - | 0.03 g/d increase | [NR] | RPL23P10 | Obesity-related traits | energy intake | GCST001762 | 610040:16:00 | Hispanic |
| rs745580 | 3 x 10-7 | (Dinner intake, adj EER ) | 438 | - | 0.04 kcal increase | [NR] | MIR148A | Obesity-related traits | energy intake | GCST001762 | 432814:12:00 | Hispanic |
| rs12531027 | 3 x 10-7 | (HRmax ) | 34 | - | 0.04 bpm increase | [NR] | AGMO | Obesity-related traits | heart rate | GCST001762 | 783110:23:00 | Hispanic |
| rs11754509 | 3 x 10-7 | (Urinary free dopamine: creatinine) | 13 | - | 0.03 unit increase | [NR] | HMGCLL1 | Obesity-related traits | urinary metabolite measurement | GCST001762 | 1144199:00:00 | Hispanic |
| rs11627056 | 3 x 10-7 | (IL6 ) | 281 | - | 0.04 pg/mL increase | [NR] | MDGA2 | Obesity-related traits | interleukin-6 measurement | GCST001762 | 879546:21:00 | Hispanic |
| rs1056513 | 3 x 10-7 | (Lean body mass ) | 495 | - | 0.03 kg increase | [NR] | PATJ | Obesity-related traits | lean body mass | GCST001762 | 254945:31:00 | Hispanic |
| rs1056513 | 3 x 10-7 | (Fat free mass ) | 495 | - | 0.03 kg increase | [NR] | PATJ | Obesity-related traits | body composition measurement | GCST001762 | 2929202:52:00 | Hispanic |
| rs10039217 | 3 x 10-7 | (Sleep duration ) | 13 | - | 0.04 min/d increase | [NR] | HRH2, CPLX2 | Obesity-related traits | sleep measurement | GCST001762 | 926814:16:00 | Hispanic |
| rs7998314 | 4 x 10-7 | (Fat mass change ) | 487 | - | 0.04 kg/y increase | [NR] | GPC6 | Obesity-related traits | body composition measurement | GCST001762 | 1559694:16:00 | Hispanic |
| rs7998314 | 4 x 10-7 | (Fat mass deposition ) | 487 | - | 0.04 kcal/d increase | [NR] | GPC6 | Obesity-related traits | body composition measurement | GCST001762 | 1559694:16:00 | Hispanic |
| rs7916663 | 4 x 10-7 | (Height ) | 184 | - | 0.04 cm increase | [NR] | RSU1 | Obesity-related traits | body height | GCST001762 | 2362113:33:00 | Hispanic |
| rs7328464 | 4 x 10-7 | (Sedentary activity ) | 53 | - | 0.04 %awake time increase | [NR] | GPC5 | Obesity-related traits | physical activity | GCST001762 | 1321371:41:00 | Hispanic |
| rs6584202 | 4 x 10-7 | (Urinary creatinine ) | 367 | - | 0.04 mmol/d increase | [NR] | PYROXD2 | Obesity-related traits | urinary metabolite measurement | GCST001762 | 42764:38:00 | Hispanic |
| rs4871750 | 4 x 10-7 | (Bone mineral content ) | 383 | - | 0.04 kg increase | [NR] | PCAT1 | Obesity-related traits | bone density | GCST001762 | 2114837:18:00 | Hispanic |
| rs4749080 | 4 x 10-7 | (IL6 ) | 268 | - | 0.04 pg/mL increase | [NR] | RNU6-632P, MYO3A | Obesity-related traits | interleukin-6 measurement | GCST001762 | 701398:32:00 | Hispanic |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs430 | 4 x 10-7 | (Urinary free epinephrine ) | 16 | - | 0.03 nmol/d increase | [NR] | TWIST1 | Obesity-related traits | urinary metabolite measurement | GCST001762 | 1640187:06:00 | Hispanic |
| rs4072286 | 4 x 10-7 | (Eotaxin ) | 461 | - | 0.03 pg/mL increase | [NR] | MIR1302-7 | Obesity-related traits | CCL11 measurement | GCST001762 | 431240:37:00 | Hispanic |
| rs220299 | 4 x 10-7 | (HRmax ) | 373 | - | 0.05 bpm increase | [NR] | UMODL1 | Obesity-related traits | heart rate | GCST001762 | 1085647:30:00 | Hispanic |
| rs17102423 | 4 x 10-7 | (Eotaxin ) | 0.2 | - | 0.03 pg/mL increase | [NR] | LINC02324, RNU2-14P | Obesity-related traits | CCL11 measurement | GCST001762 | 278453:31:00 | Hispanic |
| rs16912210 | 4 x 10-7 | (Fat free mass change ) | 0.08 | - | 0.05 kg/y increase | [NR] | HBD, HBBP1 | Obesity-related traits | body composition measurement | GCST001762 | 3852249:10:00 | Hispanic |
| rs16839626 | 4 x 10-7 | (Fat mass change ) | 60 | - | 0.04 kg/y increase | [NR] | NBEAL1 | Obesity-related traits | body composition measurement | GCST001762 | 1173708:39:00 | Hispanic |
| rs12586774 | 4 x 10-7 | (Total cysteine ) | 94 | - | 0.03 µmol/L increase | [NR] | LINC02306 | Obesity-related traits | amino acid measurement | GCST001762 | 427686:40:00 | Hispanic |
| rs12195826 | 4 x 10-7 | (Urinary nitrogen ) | 407 | - | 0.05 g/d increase | [NR] | LINC02521, GMDS-DT | Obesity-related traits | urinary nitrogen measurement | GCST001762 | 87388:03:00 | Hispanic |
| rs12023396 | 4 x 10-7 | (IL6 ) | 181 | - | 0.03 pg/mL increase | [NR] | TRIM67, FAM89A | Obesity-related traits | interleukin-6 measurement | GCST001762 | 1530836:30:00 | Hispanic |
| rs11863065 | 4 x 10-7 | (Weight ) | 0.03 | - | 0.03 kg increase | [NR] | - | Obesity-related traits | body weight | GCST001762 | 1371569:20:00 | Hispanic |
| rs11766624 | 4 x 10-7 | (Arm span ) | 153 | - | 0.04 cm increase | [NR] | AUTS2 | Obesity-related traits | arm span | GCST001762 | 317788:56:00 | Hispanic |
| rs1151200 | 4 x 10-7 | (Birth weight ) | 419 | - | 0.06 kg increase | [NR] | TENM4 | Obesity-related traits | birth weight | GCST001762 | 3387085:27:00 | Hispanic |
| rs7665957 | 5 x 10-7 | (Sleep duration ) | 60 | - | 0.01 min/d increase | [NR] | - | Obesity-related traits | sleep measurement | GCST001762 | 2166894:07:00 | Hispanic |
| rs7355746 | 5 x 10-7 | (Urinary nitrogen ) | 14 | - | 0.04 g/d increase | [NR] | TEX41, LINC01412 | Obesity-related traits | urinary nitrogen measurement | GCST001762 | 157918:54:00 | Hispanic |
| rs4958456 | 5 x 10-7 | (Urinary free dopamine ) | 92 | - | 0.04 nmol/d increase | [NR] | CAMK2A | Obesity-related traits | urinary metabolite measurement | GCST001762 | 1546986:12:00 | Hispanic |
| rs4940203 | 5 x 10-7 | (RQmax) | 294 | - | 0.05 unit increase | [NR] | DCC | Obesity-related traits | respiratory quotient | GCST001762 | 745731:19:00 | Hispanic |
| rs433755 | 5 x 10-7 | (Total cysteine ) | 451 | - | 0.03 µmol/L increase | [NR] | SEMA5A | Obesity-related traits | amino acid measurement | GCST001762 | 877785:06:00 | Hispanic |
| rs34379766 | 5 x 10-7 | (IGFBP-3 ) | 64 | - | 0.03 ng/mL increase | [NR] | ERBB3 | Obesity-related traits | IGFBP-3 measurement | GCST001762 | 1030696:12:00 | Hispanic |
| rs2198776 | 5 x 10-7 | (BMI z-score ) | 284 | - | 0.03 SD increase | [NR] | TAFA2 | Obesity-related traits | body mass index | GCST001762 | 244337:45:00 | Hispanic |
| rs17668565 | 5 x 10-7 | (Weight z-score ) | 403 | - | 0.03 SD increase | [NR] | LDHBP3 | Obesity-related traits | body weight | GCST001762 | 2504068:22:00 | Hispanic |
| rs1624802 | 5 x 10-7 | (Ft4 ) | 0.49 | - | 0.02 ng/dL increase | [NR] | LINC02418 | Obesity-related traits | hormone measurement | GCST001762 | 934684:39:00 | Hispanic |
| rs11696845 | 5 x 10-7 | (IGFBP-3 ) | 355 | - | 0.03 ng/mL increase | [NR] | KCNK15-AS1 | Obesity-related traits | IGFBP-3 measurement | GCST001762 | 1650975:51:00 | Hispanic |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| rs11203649 | 5 x 10-7 | (Urinary free epinephrine ) | 177 | - | 0.05 nmol/d increase | [NR] | SGCZ | Obesity-related traits | urinary metabolite measurement | GCST001762 | 2409906:14:00 | Hispanic |
| rs10747502 | 5 x 10-7 | (Light activity ) | 61 | - | 0.04 %awake time increase | [NR] | PLPPR5 | Obesity-related traits | physical activity | GCST001762 | 208291:43:00 | Hispanic |
| rs7608623 | 6 x 10-7 | (Total T4 ) | 229 | - | 0.03 µg/dL increase | [NR] | KLHL29, ATAD2B | Obesity-related traits | hormone measurement | GCST001762 | 981673:57:00 | Hispanic |
| rs758970 | 6 x 10-7 | (Total T4 ) | 309 | - | 0.05 µg/dL increase | [NR] | MVB12B | Obesity-related traits | hormone measurement | GCST001762 | 2107217:14:00 | Hispanic |
| rs6942458 | 6 x 10-7 | (HRmax ) | 219 | - | 0.05 bpm increase | [NR] | CACNA2D1 | Obesity-related traits | heart rate | GCST001762 | 206566:20:00 | Hispanic |
| rs6834483 | 6 x 10-7 | (Sedentary activity ) | 17 | - | 0.03 %awake time increase | [NR] | ARAP2 | Obesity-related traits | physical activity | GCST001762 | 2931992:10:00 | Hispanic |
| rs4750211 | 6 x 10-7 | (RQmax) | 0.3 | - | 0.05 increase | [NR] | CAMK1D | Obesity-related traits | respiratory quotient | GCST001762 | 1904619:41:00 | Hispanic |
| rs405460 | 6 x 10-7 | (IGFBP-3 ) | 418 | - | 0.03 ng/mL increase | [NR] | LINC01500 | Obesity-related traits | IGFBP-3 measurement | GCST001762 | 395436:43:00 | Hispanic |
| rs1530530 | 6 x 10-7 | (Testosterone ) | 68 | - | 0.03 ng/mL increase | [NR] | TPTE2P6, ATP12A | Obesity-related traits | testosterone measurement | GCST001762 | 1369226:58:00 | Hispanic |
| rs10744816 | 6 x 10-7 | (Amylin ) | 234 | - | 0.04 pM increase | [NR] | TBX5, LINC02459 | Obesity-related traits | hormone measurement | GCST001762 | 411232:08:00 | Hispanic |
| rs1020410 | 6 x 10-7 | (Calorimeter activity ) | 268 | - | 0.04 counts/d increase | [NR] | LNPK, EXTL2P1 | Obesity-related traits | physical activity | GCST001762 | 599695:29:00 | Hispanic |
| rs10107366 | 6 x 10-7 | (Energy balance ) | 80 | - | 0.04 kcal/d increase | [NR] | ERICH5, RIDA | Obesity-related traits | energy intake | GCST001762 | 1635032:19:00 | Hispanic |
| rs987052 | 7 x 10-7 | (NEFA ) | 438 | - | 0.03 mmol/L increase | [NR] | LINC01081, LINC02135 | Obesity-related traits | fatty acid measurement | GCST001762 | 1559694:16:00 | Hispanic |
| rs9545740 | 7 x 10-7 | (TNF-a ) | 408 | - | 0.03 pg/mL increase | [NR] | - | Obesity-related traits | tumor necrosis factor-alpha measurement | GCST001762 | 1438163:33:00 | Hispanic |
| rs8050907 | 7 x 10-7 | (Total antioxidants ) | 27 | - | 0.03 mM increase | [NR] | C16orf96 | Obesity-related traits | antioxidant measurement | GCST001762 | 1358370:37:00 | Hispanic |
| rs7998314 | 7 x 10-7 | (Energy storage ) | 487 | - | 0.04 kcal/d increase | [NR] | GPC6 | Obesity-related traits | body composition measurement | GCST001762 | 60521:36:00 | Hispanic |

# APPENDIX B

In Appendix B, partially adulthood related variants are listed.

| Variant and risk allele | P-value | P-value annotation | RAF | OR | Beta | CI | Mapped gene | Reported trait | Trait(s) | Background trait(s) |
|---|---|---|---|---|---|---|---|---|---|---|
| rs8043757 | 5 x 10-110 | (Obesity class I) | 0.4 | 1.23 | - | [NR] | FTO | Obesity | obesity | - |
| rs4148325 | 5 x 10-93 | | NR | - | - | - | UGT1A7, UGT1A4, UGT1A3, UGT1A6, UGT1A9, UGT1A5, UGT1A1, UGT1A8, UGT1A10 | Bilirubin levels in extreme obesity | bilirubin measurement | obesity |
| rs1558902 | 2 x 10-81 | (Overweight) | 0.41 | 1.14 | - | [NR] | FTO | Obesity | obesity | - |
| rs7185735 | 1 x 10-79 | (Obesity class II) | 0.4 | 1.33 | - | [NR] | FTO | Obesity | obesity | - |
| rs6444444 | 5 x 10-66 | (IL-1 R AcP) | NR | - | 0.66 unit increase | [0.58-0.74] | IL1RAP | Protein levels in obesity | protein measurement | obesity |
| rs7950019 | 5 x 10-45 | (SAA) | NR | - | 1.53 unit increase | [1.32-1.74] | SAA2, ST13P5 | Protein levels in obesity | protein measurement | obesity |
| rs651821 | 9 x 10-44 | | 0.3 | 1.43 | - | [1.36-1.51] | APOA5 | Metabolically unhealthy in obesity | metabolic syndrome | obesity |
| rs6711012 | 3 x 10-40 | (Obesity class I) | 0.82 | 1.18 | - | [NR] | TMEM18, LINC01875 | Obesity | obesity | - |
| rs495828 | 9 x 10-40 | (sE-Selectin) | NR | - | 0.5 unit decrease | [0.42-0.58] | ABO, Y_RNA | Protein levels in obesity | protein measurement | obesity |
| rs1421085 | 6 x 10-39 | (Obesity class III) | 0.41 | 1.45 | - | [NR] | FTO | Obesity | obesity | - |
| rs538656 | 2 x 10-36 | (Obesity class I) | 0.24 | 1.15 | - | [NR] | MC4R, RNU4-17P | Obesity | obesity | - |
| rs4778636 | 1 x 10-35 | (IL-16) | NR | - | 0.48 unit decrease | [0.4-0.56] | IL16 | Protein levels in obesity | protein measurement | obesity |
| rs6711012 | 6 x 10-35 | (Overweight) | 0.82 | 1.11 | - | [NR] | TMEM18, LINC01875 | Obesity | obesity | - |
| rs10938397 | 3 x 10-34 | (Obesity class I) | 0.43 | 1.12 | - | [NR] | PRDX4P1, THAP12P9 | Obesity | obesity | - |
| rs2607426 | 4 x 10-34 | (MIA) | NR | - | 0.49 unit increase | [0.41-0.57] | MIA-RAB4B, SNRPA | Protein levels in obesity | protein measurement | obesity |
| rs11080369 | 2 x 10-30 | (HCC-4) | NR | - | 0.79 unit decrease | [0.65-0.93] | CCL16 | Protein levels in obesity | protein measurement | obesity |
| rs3745540 | 8 x 10-29 | (kallikrein 12) | NR | - | 0.33 unit increase | [0.27-0.39] | KLK12 | Protein levels in obesity | protein measurement | obesity |
| rs1421085 | 1 x 10-28 | | 0.4 | - | - | - | FTO | Obesity | obesity | - |
| rs1421085 | 3 x 10-28 | | 0.41 | 1.44 | - | [1.35-1.54] | FTO | Obesity (early onset extreme) | obesity | - |
| rs13130484 | 4 x 10-28 | (Overweight) | 0.43 | 01.08 | - | [NR] | PRDX4P1, THAP12P9 | Obesity | obesity | - |

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|---|---|---|---|---|---|---|---|---|---|---|
| rs10871777 | 2 x 10-27 | (Overweight) | 0.24 | 1.1 | - | [NR] | RNU4-17P, MC4R | Obesity | obesity | - |
| rs281440 | 7 x 10-27 | (sICAM-5) | NR | - | 0.3 unit decrease | [0.25-0.35] | ICAM5, ICAM4 | Protein levels in obesity | protein measurement | obesity |
| rs10732279 | 3 x 10-26 | (NPS-PLA2) | NR | - | 0.38 unit increase | [0.31-0.45] | PLA2G2A | Protein levels in obesity | protein measurement | obesity |
| rs8050136 | 3 x 10-26 | | 0.60 | - | 0.06 % decrease | [NR] | FTO | Adiposity | obesity | - |
| rs10189761 | 6 x 10-24 | (Obesity class II) | 0.82 | 1.24 | - | [NR] | TMEM18, LINC01875 | Obesity | obesity | - |
| rs4962144 | 7 x 10-23 | (ATS13) | NR | - | 0.34 unit decrease | [0.27-0.41] | REXO4 | Protein levels in obesity | protein measurement | obesity |
| rs633715 | 9 x 10-23 | (Obesity class I) | 0.19 | 1.12 | - | [NR] | LINC01741, SEC16B | Obesity | obesity | - |
| rs11152213 | 3 x 10-22 | (Obesity class II) | 0.24 | 1.19 | - | [NR] | RNU4-17P | Obesity | obesity | - |
| rs2030323 | 3 x 10-22 | (Obesity class I) | 0.79 | 1.12 | - | [NR] | BDNF | Obesity | obesity | - |
| rs2206277 | 5 x 10-22 | (Obesity class I) | 0.18 | 1.12 | - | [NR] | TFAP2B | Obesity | obesity | - |
| rs13294 | 7 x 10-22 | (ECM1) | NR | - | 0.2 unit decrease | [0.16-0.24] | ECM1 | Protein levels in obesity | protein measurement | obesity |
| rs972317 | 7 x 10-22 | (PARC) | NR | - | 0.5 unit increase | [0.4-0.6] | CCL23, CCL18 | Protein levels in obesity | protein measurement | obesity |
| rs7138803 | 1 x 10-20 | (Obesity class I) | 0.38 | 01.09 | - | [NR] | BCDIN3D, RPL35AP28 | Obesity | obesity | - |
| rs633715 | 7 x 10-20 | (Overweight) | 0.2 | 01.08 | - | [NR] | LINC01741, SEC16B | Obesity | obesity | - |
| rs2207139 | 3 x 10-19 | (Obesity class II) | 0.18 | 1.2 | - | [NR] | FTH1P5, RPS17P5 | Obesity | obesity | - |
| rs633715 | 4 x 10-19 | (Obesity class II) | 0.19 | 1.19 | - | [NR] | LINC01741, SEC16B | Obesity | obesity | - |
| rs1558902 | 5 x 10-19 | | NR | 1.37 | - | [1.26-1.50] | FTO | Obesity (early onset extreme) | obesity | - |
| rs13130484 | 3 x 10-18 | (Obesity class II) | 0.43 | 1.14 | - | [NR] | PRDX4P1, THAP12P9 | Obesity | obesity | - |
| rs1421085 | 7 x 10-18 | (children) | 0.4 | 1.39 | - | [1.27-1.51] | FTO | Obesity | obesity | - |
| rs10182181 | 1 x 10-17 | (Obesity class I) | 0.46 | 01.08 | - | [NR] | DNAJC27, ADCY3 | Obesity | obesity | - |
| rs7141420 | 1 x 10-17 | (Obesity class I) | 0.52 | 01.08 | - | [NR] | NRXN3 | Obesity | obesity | - |
| rs7531118 | 2 x 10-17 | (Obesity class I) | 0.56 | 01.08 | - | [NR] | RPL31P12, RNU6-1246P | Obesity | obesity | - |
| rs3765964 | 3 x 10-17 | (Carbonic anhydrase 6) | NR | - | 0.44 unit increase | [0.34-0.54] | CA6 | Protein levels in obesity | protein measurement | obesity |
| rs2030323 | 5 x 10-17 | (Overweight) | 0.79 | 01.07 | - | [NR] | BDNF | Obesity | obesity | - |
| rs988712 | 5 x 10-17 | | 0.75 | 1.36 | - | [1.20-1.55] | BDNF-AS | Obesity | obesity | - |
| rs7138803 | 1 x 10-16 | (Obesity class II) | 0.38 | 1.14 | - | [NR] | BCDIN3D, RPL35AP28 | Obesity | obesity | - |
| rs1421085 | 2 x 10-16 | | 125 | 1.18 | - | [1.13-1.22] | FTO | Obesity | obesity | - |
| rs2568958 | 4 x 10-16 | (Overweight) | 0.61 | 01.06 | - | [NR] | RPL31P12, NEGR1 | Obesity | obesity | - |

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|---|---|---|---|---|---|---|---|---|---|---|
| rs1329428 | 5 x 10-16 | (Factor H) | NR | - | 0.08 unit increase | [0.062-0.098] | CFH | Protein levels in obesity | protein measurement | obesity |
| rs2206277 | 7 x 10-16 | (Overweight) | 0.18 | 01.07 | - | [NR] | TFAP2B | Obesity | obesity | - |
| rs11671930 | 1 x 10-15 | (TECK) | NR | - | 0.5 unit decrease | [0.38-0.62] | CCL25 | Protein levels in obesity | protein measurement | obesity |
| rs2000999 | 3 x 10-15 | (Haptoglobin mixed) | NR | - | 0.49 unit decrease | [0.37-0.61] | TXNL4B, HPR | Protein levels in obesity | protein measurement | obesity |
| rs17782313 | 5 x 10-15 | | 0.18 | - | - | - | MC4R, RNU4-17P | Obesity | obesity | - |
| rs7851696 | 5 x 10-15 | (FCN2) | NR | - | 0.38 unit decrease | [0.28-0.48] | FCN2 | Protein levels in obesity | protein measurement | obesity |
| rs9816226 | 2 x 10-14 | (Overweight) | 0.82 | 01.07 | - | [NR] | DGKG | Obesity | obesity | - |
| rs10182181 | 3 x 10-14 | (Overweight) | 0.46 | 01.05 | - | [NR] | DNAJC27, ADCY3 | Obesity | obesity | - |
| rs1800437 | 3 x 10-14 | (Obesity class I) | 0.78 | 1.1 | - | [NR] | GIPR | Obesity | obesity | - |
| rs16917237 | 8 x 10-14 | | NR | 1.11 | - | - | BDNF, BDNF-AS | COVID-19 or obesity (pleiotropy) | COVID-19, obesity | - |
| rs476828 | 9 x 10-14 | | 0.24 | 1.33 | - | [1.23-1.43] | MC4R, RNU4-17P | Obesity (early onset extreme) | obesity | - |
| rs5510 | 9 x 10-14 | (Kallistatin) | NR | - | 0.11 unit increase | [0.083-0.137] | SERPINA4, SERPINA5 | Protein levels in obesity | protein measurement | obesity |
| rs3101336 | 1 x 10-13 | (Obesity class II) | 0.61 | 1.12 | - | [NR] | RPL31P12, NEGR1 | Obesity | obesity | - |
| rs3806702 | 1 x 10-13 | (Cripto) | NR | - | 0.14 unit increase | [0.1-0.18] | TDGF1, LRRC2 | Protein levels in obesity | protein measurement | obesity |
| rs12463617 | 2 x 10-13 | | 0.85 | 1.42 | - | [1.29-1.56] | TMEM18, LINC01875 | Obesity (early onset extreme) | obesity | - |
| rs6036507 | 2 x 10-13 | (CYTN) | NR | - | 0.31 unit increase | [0.23-0.39] | CST2P1, CST1 | Protein levels in obesity | protein measurement | obesity |
| rs9816226 | 2 x 10-13 | (Obesity class I) | 0.82 | 1.1 | - | [NR] | DGKG | Obesity | obesity | - |
| rs7498665 | 3 x 10-13 | (Obesity class I) | 0.4 | 01.07 | - | [NR] | SH2B1 | Obesity | obesity | - |
| rs10423928 | 4 x 10-13 | (Obesity class II) | 0.77 | 1.16 | - | [NR] | GIPR | Obesity | obesity | - |
| rs1424233 | 4 x 10-13 | | 0.43 | - | - | - | MAF, LINC01229 | Obesity | obesity | - |
| rs1421085 | 5 x 10-13 | (adults) | 0.41 | 1.25 | - | [1.10-1.40] | FTO | Obesity | obesity | - |
| rs1993709 | 5 x 10-13 | | 0.81 | 1.38 | - | [1.26-1.50] | RPL31P12 | Obesity (early onset extreme) | obesity | - |
| rs8028313 | 6 x 10-13 | (Obesity class I) | 0.78 | 01.08 | - | [NR] | MAP2K5 | Obesity | obesity | - |
| rs17817449 | 2 x 10-12 | (obesity) | NR | - | - | - | FTO | Obesity | obesity | - |
| rs2307111 | 3 x 10-12 | (Obesity class I) | 0.6 | 01.07 | - | [NR] | POC5 | Obesity | obesity | - |
| rs11599750 | 4 x 10-12 | (Calpastatin) | NR | - | 0.2 unit decrease | [0.16-0.24] | CPN1 | Protein levels in obesity | protein measurement | obesity |
| rs12446554 | 4 x 10-12 | (Overweight) | 0.86 | 01.07 | - | [NR] | GPRC5B, GPR139 | Obesity | obesity | - |
| rs7498665 | 5 x 10-12 | (Overweight) | 0.4 | 01.05 | - | [NR] | SH2B1 | Obesity | obesity | - |

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|---|---|---|---|---|---|---|---|---|---|---|
| rs9941349 | 6 x 10-12 | | 0.43 | 1.48 | - | [1.33-1.66] | FTO | Obesity (extreme) | obesity | - |
| rs4586493 | 8 x 10-12 | (WFKN2) | NR | - | 0.18 unit increase | [0.13-0.23] | WFIKKN2, RPL5P33 | Protein levels in obesity | protein measurement | obesity |
| rs17024258 | 9 x 10-12 | (Obesity class I) | 0.04 | 1.25 | - | [NR] | GNAT2 | Obesity | obesity | - |
| rs11042023 | 1 x 10-11 | (Obesity class I) | 0.65 | 01.07 | - | [NR] | TRIM66 | Obesity | obesity | - |
| rs1461674 | 1 x 10-11 | (Contactin-5) | NR | - | 0.23 unit increase | [0.16-0.3] | CNTN5 | Protein levels in obesity | protein measurement | obesity |
| rs6036507 | 1 x 10-11 | (CYTT) | NR | - | 0.3 unit increase | [0.21-0.39] | CST2P1, CST1 | Protein levels in obesity | protein measurement | obesity |
| rs8028313 | 1 x 10-11 | (Overweight) | 0.79 | 01.06 | - | [NR] | MAP2K5 | Obesity | obesity | - |
| rs972317 | 1 x 10-11 | (MIP-1a) | NR | - | 0.35 unit increase | [0.25-0.45] | CCL23, CCL18 | Protein levels in obesity | protein measurement | obesity |
| rs10105606 | 2 x 10-11 | | 0.12 | 0.83 | - | [0.78-0.87] | RPL30P9, LPL | Metabolically unhealthy in obesity | metabolic syndrome | obesity |
| rs987237 | 2 x 10-11 | (WC) | 164 | - | 0.04 z-score unit increase | [0.03-0.05] | TFAP2B | Adiposity | obesity | - |
| rs13078807 | 3 x 10-11 | (Overweight) | 0.2 | 01.06 | - | [NR] | CADM2 | Obesity | obesity | - |
| rs541862 | 3 x 10-11 | (Factor B) | NR | - | 0.15 unit increase | [0.1-0.2] | CFB | Protein levels in obesity | protein measurement | obesity |
| rs2943650 | 4 x 10-11 | | 0.64 | - | 0.03 % decrease | [NR] | NYAP2, MIR5702 | Adiposity | obesity | - |
| rs17700144 | 6 x 10-11 | | NR | 1.22 | - | [1.09-1.37] | RPS3AP49, RNU6-567P | Obesity (early onset extreme) | obesity | - |
| rs2030323 | 6 x 10-11 | (Obesity class II) | 0.79 | 1.13 | - | [NR] | BDNF | Obesity | obesity | - |
| rs2074639 | 6 x 10-11 | (Proteinase-3) | NR | - | 0.22 unit increase | [0.16-0.28] | PRTN3, AZU1 | Protein levels in obesity | protein measurement | obesity |
| rs7103402 | 7 x 10-11 | (FCN2) | NR | - | 0.3 unit decrease | [0.2-0.4] | NXPE2P1, NXPE1 | Protein levels in obesity | protein measurement | obesity |
| rs887912 | 1 x 10-10 | (Obesity class I) | 0.28 | 01.07 | - | [NR] | LINC01122 | Obesity | obesity | - |
| rs10282458 | 2 x 10-10 | (TIG2) | NR | - | 0.12 unit increase | [0.085-0.155] | REPIN1-AS1, RARRES2 | Protein levels in obesity | protein measurement | obesity |
| rs10875976 | 2 x 10-10 | (Overweight) | 0.49 | 01.04 | - | [NR] | BCDIN3D-AS1 | Obesity | obesity | - |
| rs12446632 | 2 x 10-10 | (Obesity class I) | 0.86 | 01.09 | - | [NR] | GPRC5B, GPR139 | Obesity | obesity | - |
| rs1412239 | 2 x 10-10 | (Obesity class II) | 0.32 | 1.11 | - | [NR] | LINGO2 | Obesity | obesity | - |
| rs821840 | 2 x 10-10 | | 0.17 | 0.83 | - | [0.78-0.88] | CETP, HERPUD1 | Metabolically unhealthy in obesity | metabolic syndrome | obesity |
| rs12876365 | 3 x 10-10 | (MP2K2) | NR | - | 0.2 unit decrease | [0.14-0.26] | CUL4A | Protein levels in obesity | protein measurement | obesity |
| rs1957894 | 3 x 10-10 | | 0.06 | 1.5 | - | [1.32-1.70] | PRKCH | Obesity (early onset extreme) | obesity | - |
| rs2116830 | 3 x 10-10 | | 0.80 | 1.26 | - | [1.12-1.41] | KCNMA1 | Obesity | obesity | - |
| rs972317 | 3 x 10-10 | (LD78-beta) | NR | - | 0.2 unit increase | [0.14-0.26] | CCL23, CCL18 | Protein levels in obesity | protein measurement | obesity |

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|---|---|---|---|---|---|---|---|---|---|---|
| rs13200531 | 4 x 10-10 | (Angiotensinogen) | NR | - | 0.22 unit decrease | [0.15-0.29] | - | Protein level change in low calorie diet obesity intervention | response to low calorie diet, protein measurement | obesity |
| rs4735692 | 4 x 10-10 | (Overweight) | 0.58 | 01.04 | - | [NR] | - | Obesity | obesity | - |
| rs3136673 | 6 x 10-10 | | NR | 01.06 | - | - | CCR3 | COVID-19 or obesity (pleiotropy) | COVID-19, obesity | - |
| rs7189927 | 6 x 10-10 | | NR | 01.07 | - | - | ATP2A1 | COVID-19 or obesity (pleiotropy) | COVID-19, obesity | - |
| rs1541984 | 7 x 10-10 | | NR | 01.07 | - | - | ADCY3 | COVID-19 or obesity (pleiotropy) | COVID-19, obesity | - |
| rs1886748 | 7 x 10-10 | (HAI-1) | NR | - | 0.2 unit decrease | [0.14-0.26] | MYCBP | Protein levels in obesity | protein measurement | obesity |
| rs8050136 | 8 x 10-10 | | - | 1.51 | - | [1.37-1.65] | FTO | Obesity (extreme) | obesity | - |
| rs11588887 | 1 x 10-9 | | - | 1.68 | - | NR | DUSP23, CRP | Serum C-reactive protein concentration in obesity | C-reactive protein measurement | obesity |
| rs10860794 | 2 x 10-9 | (CATZ) | NR | - | 0.1 unit decrease | [0.061-0.139] | GNPTAB | Protein levels in obesity | protein measurement | obesity |
| rs11208659 | 2 x 10-9 | | 0.08 | 1.42 | - | [1.27-1.59] | LEPR | Obesity (early onset extreme) | obesity | - |
| rs12042360 | 2 x 10-9 | | - | 1.52 | - | NR | CRP, DUSP23 | Serum C-reactive protein concentration in visceral obesity (waist circumference) | C-reactive protein measurement | obesity |
| rs4735692 | 2 x 10-9 | (Obesity class I) | 0.58 | 01.06 | - | [NR] | - | Obesity | obesity | - |
| rs564343 | 2 x 10-9 | | 0.41 | 1.22 | - | [1.15-1.31] | PACS1 | Obesity (early onset extreme) | obesity | - |
| rs6731302 | 2 x 10-9 | (Overweight) | 0.44 | 01.04 | - | [NR] | LINC01122 | Obesity | obesity | - |
| rs7661253 | 2 x 10-9 | (IDS) | NR | - | 0.2 unit decrease | [0.14-0.26] | TENM3-AS1 | Protein levels in obesity | protein measurement | obesity |