

**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 yollar üzerindeki etkilerini, çocukluk ve erişkinlik obezite ilişkili yollar 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 mammals 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 lower 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 ghrelin 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).

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 $p < 1 \times 10^{-6}$ (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 $p < 1 \times 10^{-6}$ 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. For this analysis SNP Nexus annotation tool (URL2) was used (Oscanoa, J. 2018). Threshold $p < 1 \times 10^{-8}$ 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 $p < 1 \times 10^{-8}$ 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 $p < 1 \times 10^{-6}$, 142 variants that have $p < 1 \times 10^{-8}$ 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 $p < 1 \times 10^{-8}$ 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).

Karyotype of genomic consequences



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).

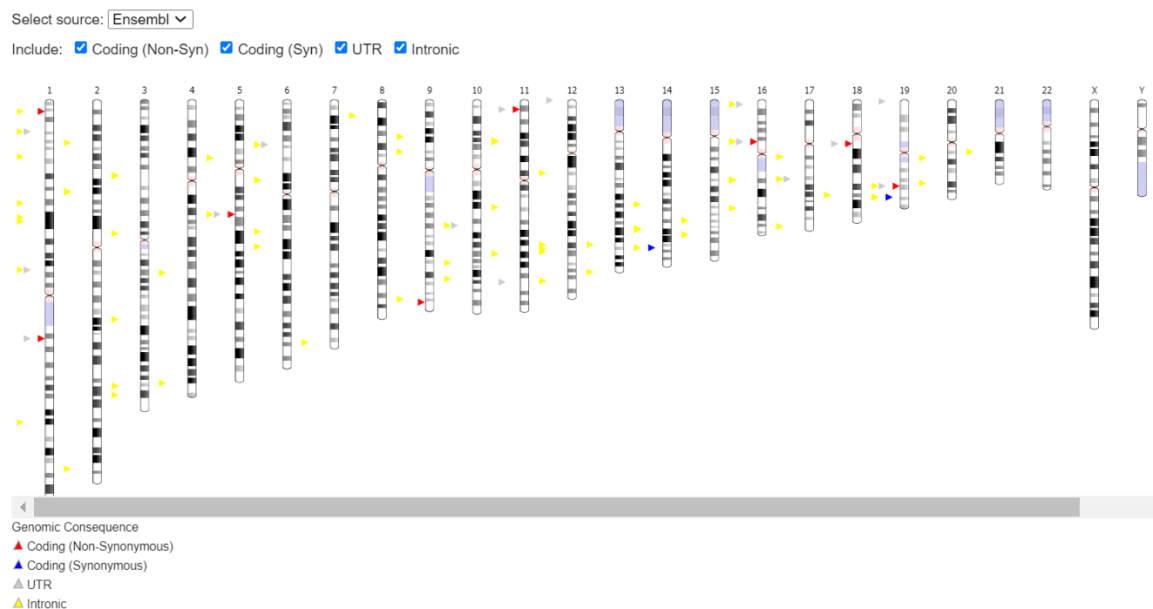


Figure 3.2 Distribution of adulthood obesity related SNPs on human chromosomes

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 nearest genes. The analysis provided the whole results. Processed pseudogene, lincRNA, snRNA, protein coding genes, miRNA, bidirectional promoter lincRNA, 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	CHRNA4, 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			

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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 R² results. R² > 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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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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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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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).

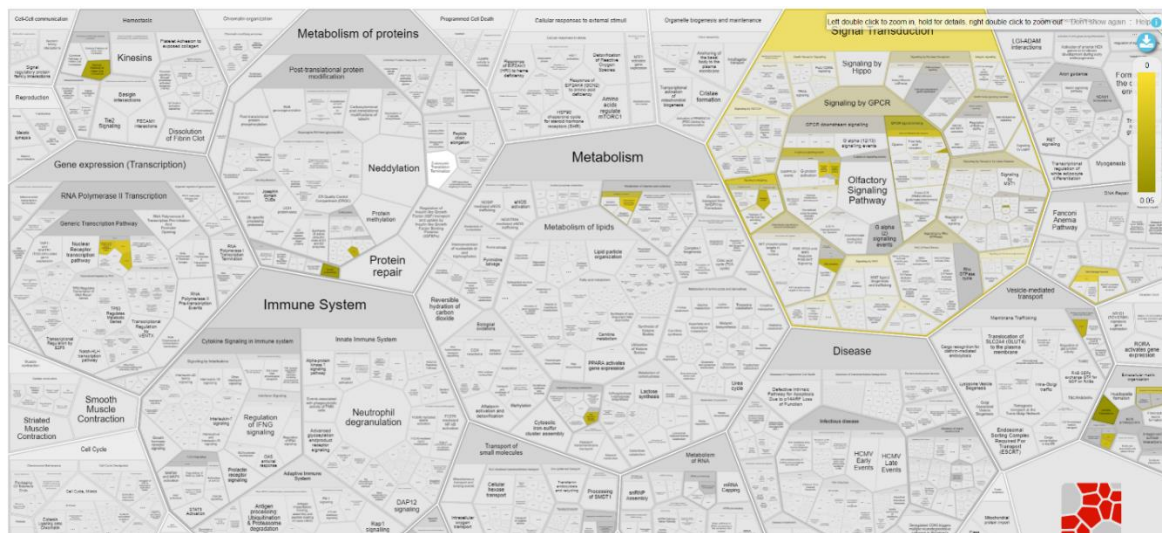


Figure 3.3 Childhood obesity related genes pathway analysis

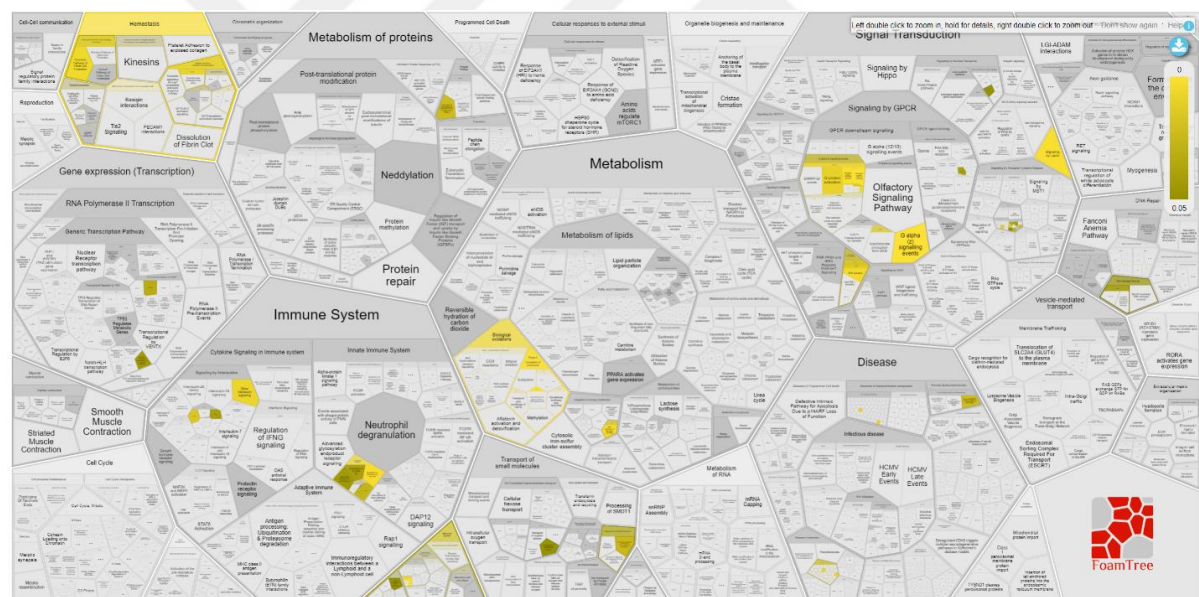


Figure 3.4 Adulthood obesity related genes pathway analysis

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.

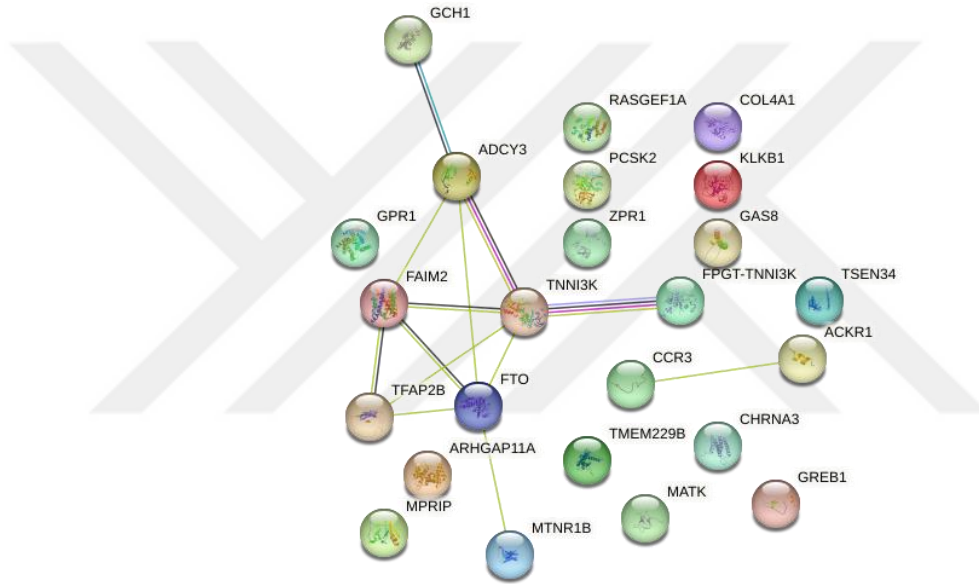


Figure 3.5 Childhood obesity related proteins network analysis

In Figure 3.5 within childhood obesity related proteins, *GCH1*, *ADCY3*, *FAIM2*, *TNNI3K*, *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).

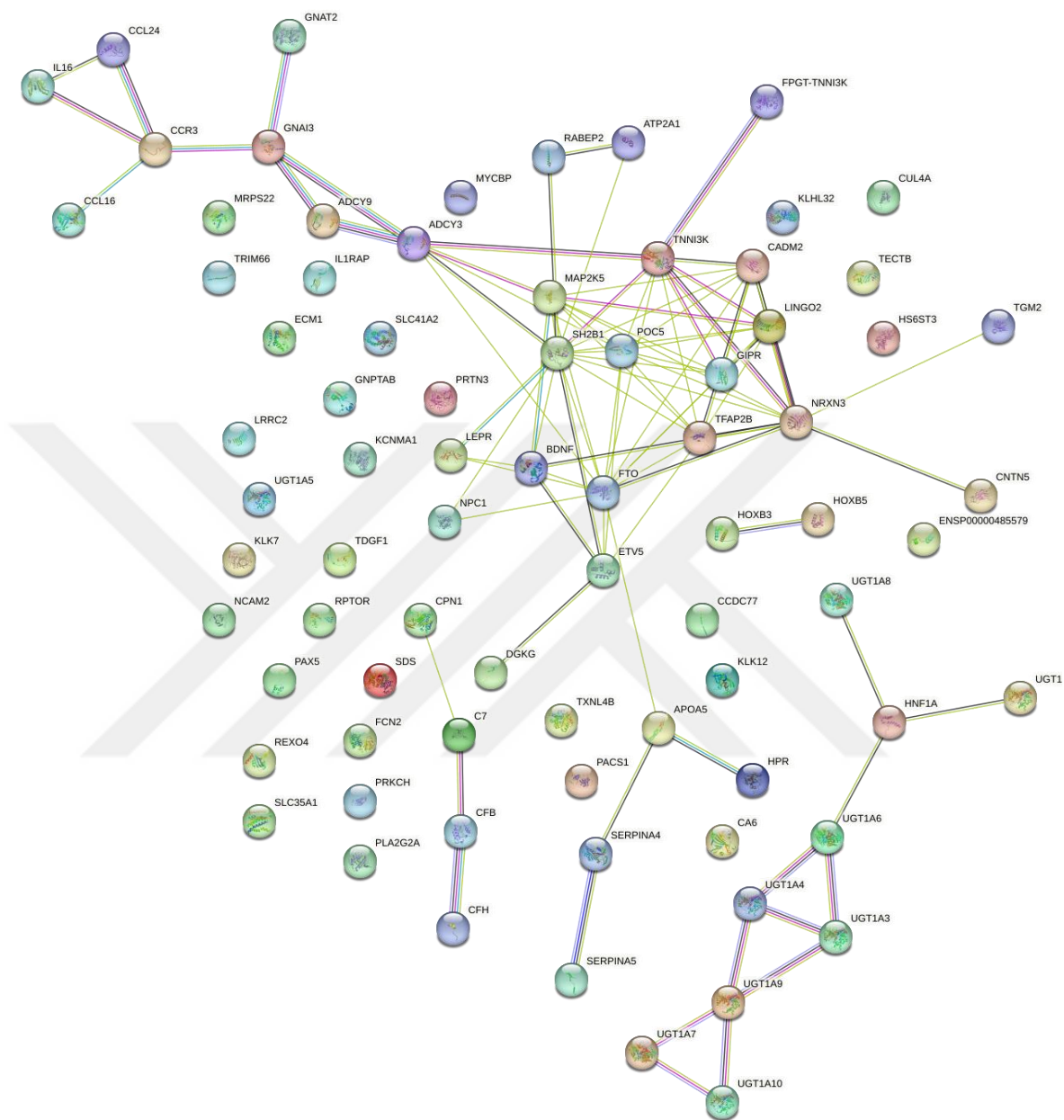


Figure 3.6 Adulthood obesity related proteins network analysis

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

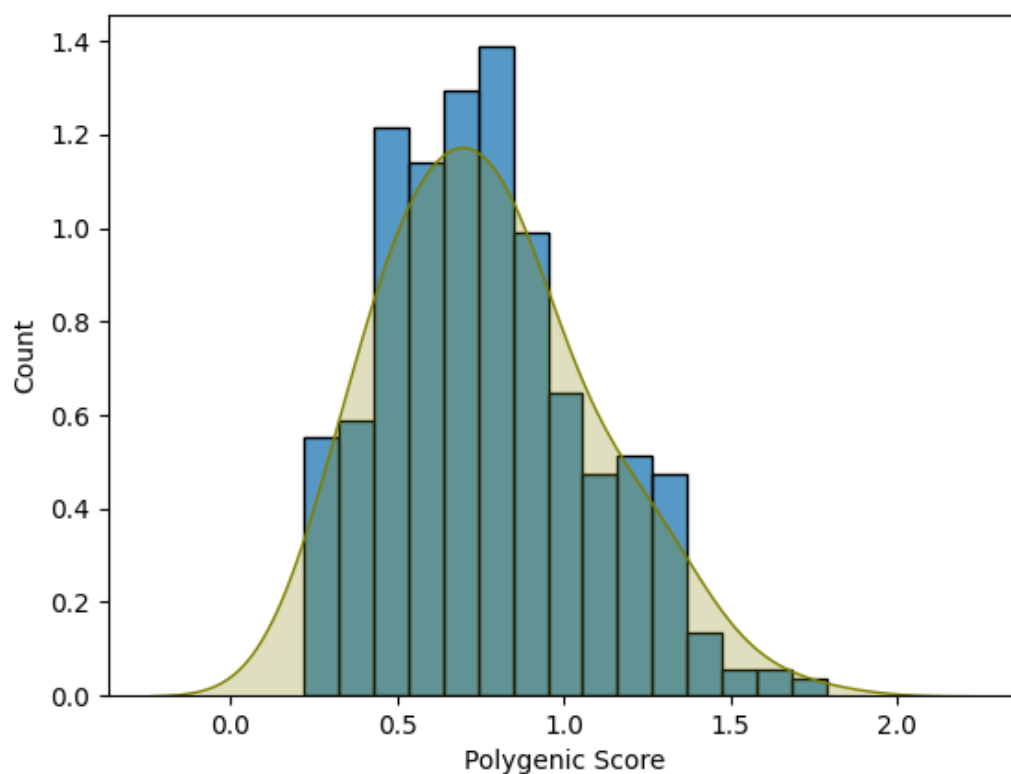


Figure 3.7 Polygenic Risk Score calculation results from childhood obesity related variants

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. *TNNI3K*, 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

rs6174486 2	7 x 10-8	(IGFBP-3)	41	-	0.04 ng/mL increase	[NR]	MPRIIP	Obesity- related traits	IGFBP-3 measurement	GCST00176 2	286098:08:00	Hispanic
rs6044834	8 x 10-8	(Total antioxidants)	69	-	0.04 mM increase	[NR]	PCSK2	Obesity- related traits	antioxidant measurement	GCST00176 2	346573:34:00	Hispanic
rs1693300 6	8 x 10-8	(Light activity)	0.11	-	0.04 min/d increase	[NR]	TTC39B, RPL7P33	Obesity- related traits	physical activity	GCST00176 2	351807:59:00	Hispanic
rs1197426 9	8 x 10-8	(Urinary creatinine)	128	-	0.05 mmol/d increase	[NR]	LINC01162	Obesity- related traits	urinary metabolite measurement	GCST00176 2	255607:36:00	Hispanic
rs1013114 1	8 x 10-8	(Urinary nitrogen)	0.28	-	0.04 g/d increase	[NR]	RNASE1, RNASE6	Obesity- related traits	urinary nitrogen measurement	GCST00176 2	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	GCST00176 2	3103952:00:0 0	Hispanic
rs6061910	1 x 10-7	(IGFBP-3)	63	-	0.04 ng/mL increase	[NR]	CDH4	Obesity- related traits	IGFBP-3 measurement	GCST00176 2	1031911:26:0 0	Hispanic
rs589756	1 x 10-7	(Lean body mass)	129	-	0.04 kg increase	[NR]	MOXD1	Obesity- related traits	lean body mass	GCST00176 2	1438931:20:0 0	Hispanic
rs589756	1 x 10-7	(Fat free mass)	129	-	0.04 kg increase	[NR]	MOXD1	Obesity- related traits	body composition measurement	GCST00176 2	2205372:18:0 0	Hispanic
rs5863270 0	1 x 10-7	(Free T3)	77	-	0.05 pg/mL increase	[NR]	SLC27A5, ZNF446	Obesity- related traits	hormone measurement	GCST00176 2	2205372:18:0 0	Hispanic
rs4083242	1 x 10-7	(Sedentary&ligh t activity)	336	-	0.03 min/d increase	[NR]	LINC00917	Obesity- related traits	physical activity	GCST00176 2	974696:14:00	Hispanic
rs1186306 5	1 x 10-7	(Hip circumference)	0.03	-	0.04 cm increase	[NR]	-	Obesity- related traits	hip circumference	GCST00176 2	1032238:44:0 0	Hispanic
rs1056513	1 x 10-7	(Weight)	495	-	0.03 kg increase	[NR]	PATJ	Obesity- related traits	body weight	GCST00176 2	1371569:20:0 0	Hispanic
rs7654585	2 x 10-7	(WC change)	374	-	0.04 cm/y increase	[NR]	SMIM20	Obesity- related traits	waist circumference	GCST00176 2	1031911:26:0 0	Hispanic
rs7650267	2 x 10-7	(Eotaxin)	93	-	0.04 pg/mL increase	[NR]	ANO10	Obesity- related traits	CCL11 measurement	GCST00176 2	1031911:26:0 0	Hispanic
rs4356975	2 x 10-7	(Gestational age)	295	-	0.07 wk increase	[NR]	UGT2B7	Obesity- related traits	gestational age	GCST00176 2	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	GCST00176 2	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	GCST00176 2	1151783:05:0 0	Hispanic
rs333960	2 x 10-7	(QUICKI)	144	-	0.04 unit increase	[NR]	LINC01768, CSF1	Obesity- related traits	insulin sensitivity measurement	GCST00176 2	1396724:30:0 0	Hispanic
rs1913185	2 x 10-7	(NEFA)	249	-	0.04 mmol/L increase	[NR]	PLSCR4, PLOD2	Obesity- related traits	fatty acid measurement	GCST00176 2	2436180:50:0 0	Hispanic
rs1683962 6	2 x 10-7	(Energy storage)	60	-	0.05 kcal/d increase	[NR]	NBEAL1	Obesity- related traits	body composition measurement	GCST00176 2	2011777:44:0 0	Hispanic
rs1683962 6	2 x 10-7	(Fat mass deposition)	60	-	0.05 kcal/d increase	[NR]	NBEAL1	Obesity- related traits	body composition measurement	GCST00176 2	1831615:18:0 0	Hispanic

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

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

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	-

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	-

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	-

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]	WFIKK2, 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

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	-
rs1158887	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