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Integration and Weighing of Omics Data for Obesity

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Abstract

Objective: OMICs research has become of great interest over the last years and enabled the research community to acquisition an increasing amount of data. In a prior study by our group, we have employed a novel positional integrative approach. For this second study we utilized the same integration method but weighed each individual data source trying to verify our already found regions and/or identify new gene regions of interest for obesity.

Method: In contrast to previous methodologies employed for integration of heterogeneous OMIC data, we based the integration on genomic positions of alterations in human disease and employed an additional weighing step. A data search for various types of studies on Obesity (genome-wide association, meta-analysis, transcriptomic, proteomic studies and epigenetic studies) was conducted to establish the initial data set. For this study, five different weighing settings were used, to individually double the input of genomic data, transcriptomic data, proteomic data, microRNA data and epigenetic data in comparison to all the other data sources.

Results and discussion: The analysis identified ten gene regions (ATP5O, ALK7, GAPDH, IFFO1, NCAPD2, DDX50, MAOB, ATM, STOX1 and PRRC2A). ATP5O, ALK7 and GADPH were also identified in our prior study as the highest scoring gene regions and prove to be consistent in our data set. Even though, the ten high ranked and discussed genes could not be directly linked to obesity nine of them are associated with Type 2 Diabetes or a neurodegenerative disease. Both disorders show a higher prevalence in obese individuals compared to lean.

Conclusion: In this study, we applied a new method of positional integrational analysis of different OMIC-layers and an additional validation step through weighing. our study provides a basis for further research to elucidate underlying mechanisms of these associations and identify new targets for preventive and therapeutic interventions.

Keywords: Obesity; OMIC-data integration; Data weighing

Objective

In the last years emerging fields of biology were added the suffix '-omics' onto previously used terms, such as genomics, transcriptomics, proteomics and epigenomics. The related suffix -ome is used to address the objects of study of such fields and refers to the collective characterization of all molecules or mechanisms on a distinct level of metabolic processes [1]. Analysis of OMICs Data aims to investigate and identify the pathways and biological processes most affected in the datasets and to highlight potential biomarkers and drug targets. OMICs research has become of great interest over the last years and enabled the research community to acquisition an increasing amount of data. These data comprehensively measure complex and multilayered molecular networks and provide a snapshot of biological processes in a cell, organism, or their communities. Functional analysis is already used in personalized medicine, patient stratification and drug repositioning, in many areas of public health.

OMICs data analysis depends on knowledge of pathway maps, protein interactions, functional ontologies, and gene-disease associations, which can be achieved by advanced analytical algorithms for enrichment or network analysis [2-4].

Obesity (BMI>30 kg/m^2) has become an enormous public health problem that affects millions of people all around the globe [5-7]. Obesity is involved in the pathogenesis of diseases like hypertension, cardiovascular events, metabolic syndrome, diabetes mellitus type 2 [8,9], and different types of cancer [10-12]. Over the last decade studies have shown that the etiology of obesity is multifactorial and includes a combination of genetic and environmental factors that influence the balance between energy intake and energy release [13-16]. Tremendous effort is made to better understand the complex genetics of human obesity and utilize the discovered knowledge about the signaling pathways of obesity to design obesity drugs and novel therapies [17,18]. Obesity appears to be in part under genetic control, with a multitude of genes, most with a modest effect, contributing to an individual's predisposition to obesity [19]. It is estimated that 40% to 70% of human fat mass is heritable [20]. Genome-wide scans have led to the identification of several chromosome regions that are likely to harbor genes determining susceptibility and indicate that at least 32 genes contribute to common forms of obesity. These genes are thought to be related through the earlier discussed biochemical mechanisms that are implicated in metabolic diseases.

One example is the transcription factor 7-like 2 (TCF7L2) gene. TCF7L2 encrypts a transcription factor that is implicated in the Wnt signaling pathway and is found to be identified in many tissues, including those with a key metabolic role [21]. Though various cell or animal studies showed persuasive evidence for a powerful association of TCF7L2 into pancreatic beta cell mechanisms including insulin production and processing [22], some studies also introduced the possibility that the beta cell dysfunction related to TCF7L2 was indirect and was the final result of disruptions in liver, brain, or gut [23,24].

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It has been identified that the strongest genetic association with risk to polygenic obesity are single-nucleotide variants in intron 1 and 2 of the FTO (fat mass and obesity associated) gene [25,26]. FTO has attracted interest as it was identified by genome-wide studies as a susceptibility gene for body mass index (BMI) and T2DM. BMI is a measure of obesity, strongly suggesting that the association of FTO gene variations with T2DM risk is secondary to effects on BMI. Extensive molecular studies using experimental animal models, "forward genetics" (e.g. generation of random mutations and screening for phenotypes of interest), and "reverse genetics" (e.g. generation mutations in a gene of interest and observing the resulting phenotypes) have helped identify critical pathways that regulate body fat and food intake [27]. An example is the central melanocortin pathway that has a fundamental importance in mammalian energy balance [28]. As a result of these extensive efforts, human ortholog genes were identified as well [29].

While several genes have been linked to excess weight gain, the existence of these genes cannot explain the rapidly growing prevalence of obesity. Many explanations for this missing heritability have been investigated in recent years, including much larger numbers of variants of smaller effect yet to be found, rarer variants that are poorly detected by available genotyping arrays or structural variants poorly depicted by existing arrays. Also low power to detect gene–gene interactions and inadequate accounting for shared environment among relatives. Therefore, epigenetics literally means "on top of or in addition to genetics" became of greater interest in the last couple of years. It is defined as the study of mechanisms or pathways that initiate and maintain heritable patterns of gene expression and gene function without changing the DNA sequence. In parallel to the term "genome" that defines the complete set of genetic information contained in the DNA of an organism, "epigenome" generally refers to the complete set of characteristics of epigenetic pathways in an organism. Epigenetic mechanisms involve chemical processes such as DNA methylation, covalent modifications to histones, and chromatin folding that can change gene expression without changing the DNA sequence [30]. Epigenetic alterations can sometimes promote expression of a gene that has typically been silent or silence a gene that is usually active. A well studied example is the Dutch famine that describes the effects of prenatal exposure to a famine on health in later life. It was found that undernutrition during gestation affects health in later life and that this effects depend on the time point of exposure [31].

For common multifactorial traits like obesity, GWAS have been very informative but do not address the heritable risk sufficiently. Rarer variants or epigenetic investigations are important but in general, more integrated approaches are needed in which environmental risk factors are considered and combined with functional genomic analyses.

We already utilized an approach for integration of such multi-origin data based on positions of genetic alterations occurring in obesity [32,33]. For this second study we utilized the same data set but weighed each individual data source double and combined them with all the other data sources weighed single, which means we conducted 5 different analysis (genomic, transcriptomic, proteomic, RNA data, epigenetic) with the integration tool trying to verify our already found regions and/or identify new gene regions of interest.

Method

We utilized the same data set we used for our prior study [32] which we generated through a search for various types of studies on Obesity (genome-wide association, meta-analysis, transcriptomic, proteomic studies, microRNA data and epigenetic studies) in online repositories, using GWAS Central (http://www.gwascentral.org) Medline database (www.ncbi.nlm.nih.gov/pubmed/) with search string (obesity) and (transcriptome OR proteome OR genome-wide OR microarray OR profiling OR epigenetics). Additionally, Gene Expression Omnibus (GEO) repository (http://www.ncbi.nlm.nih.gov/geo/), ArrayExpress (http://www.ebi.ac.uk/arrayexpress/) and Stanford Microarray Database (http://smd.stanford.edu) were searched up to find more suitable sources of data for inclusion in our data set. Studies that were conducted in adults (male and female) of any ethnic origin were included in the data set. Studies conducted in animals, children or elderly, and studies missing information of gender, age, study design and ethnicity were excluded from the data set. The data search was started from the Jan 01, 2000 to Jan 01, 2014 [32].

GWAS and meta-analysis

Data from 20 GWA Studies and two Meta-Analysis were obtained and are listed in Table 1 [33-54].

Transcriptional data

Raw data on transcriptomic alterations in adipose, omental, and subcutaneous fat, as well as in liver and in skeletal muscle were obtained from GEO repository. Transcriptomic alterations were treated as separate data sets to account for possible differences in transcriptional alterations observed in these tissue samples [55-62].

Proteomic, microRNA data and epigenetics

We have included three studies investigating proteomic, microRNA and epigenetic alterations by Arner et al. [61], Farha et al. [63] and Barres et al. [64]. The three studies were treated as separate data sets to account for their different biological layer and the different tissues samples that were utilized for the analysis.

The positional integration approach was introduced by Maver et al. [65] in 2011. To utilize the bioinformatical tool the p-value of each signal is transformed to $-\log_{10}$p value and all annotations are converted to coordinate positions. Then the tool arranges the significant signals from every type of study into the selected intervals on the DNA backbone [65]. The tool allows the user to weigh the different data sets and select the kb length. Weighing settings were adjusted and a 50 kb length was selected. For this study, 5 different weighing settings were used, to individually double the input of genomic data, transcriptomic data, proteomic data, microRNA data and epigenetic data in comparison to all the other data sources. Our initial data assembly was subdivided into 50 kb regions, and signals from afore mentioned studies were arranged on the genomic backbone into the corresponding regions according to their genomic position.

Evaluation was performed by searching for corresponding genes in the different weighed data sets and a direct association of genes located in top regions selected by the integration process and obesity in the Medline database (www.ncbi.nlm.nih.gov/pubmed). The search was performed on articles that appeared in Medline using the following search string: 'Obesity AND Gene,' where 'Gene' entry represented candidate genes located in the regions discovered by the integration process.

Additionally functional profiles of genes located in the set of top region have been profiled using Gene Ontology (GO, http://www.geneontology.org [66]) and Kyoto Encyclopedia of Genes and Genomes (KEGG, http://www.genome.jp/kegg/ [67]).

Name	Number of Individuals	Analytical Method	Total Markers Imported	Related citations
GWAS of adiposity- related heterogeneity in patterns of type II diabetes susceptibility	Initial Panel 4,862 (Cases 1,924, Controls 2,938) Second Panel 9,103 (Cases 3,757, Controls 5,346)	Affymetrix 393,453	5	Timpson et al. [33] Hindorff et al. [34]
GWAS of type II diabetes mellitus	5,975 (Cases 531, Controls 5,275)	Hap300	55	Steinthorsdottir et al. [35] Johnson et al. [36]
GWAS of waist circumference in individuals of Caucasian descent	Initial Panel 31,373 Replication Panel 38,641	Affymetrix and Illumina up to 512,349	7	Heard-Costa et al. [37] Hindorff et al. [34]
GWAS of extreme obesity	3,972 (Cases 775, Controls 3,197)	Illumina 457,251	13	Cotsapas et al. [38] Hindorff et al. [34]
GWAS of body mass index	10,657	Affymetrix 490,032	1	Frayling et al. [39] Hindorff et al. [34]
GWAS of body mass index in individuals of European descent	16,876	Affymetrix 344,883	2	Loos et al. [40] Hindorff et al. [34]
GWAS of body mass index	32,387	Illumina and Affymetrix 2,399,588	11	Willer et al. [41] Hindorff et al. [34]
GWAS of body mass index and weight	80,969	Illumina 305,846	17	Thorleifsson et al. [42] Hindorff et al. [34]
GWAS of body mass index and waist circumference in the Framingham Heart Study	1,341	Affy100K	34	Fox et al. [43] Johnson et al. [36] Hindorff et al. [34]
GWAS of obesity-related traits	4,298	Affy10K Affy500K	37	Scuteri et al. [44] Johnson et [36] al. Hindorff et al. [34]
GWAS of weight and body mass index	3,925	Illumina 318,237	6	Johansson et al. [45] Hindorff et al. [34]
GWAS of extreme obesity	Initial Panel 5,373 (Cases 2,633, Controls 2,740) Replication Panel 29,181	Illumina 545,349	4	Paternoster et al. [46] Hindorff et al. [34]
GWAS of obesity	Initial Panel 1,060 (Cases 520, Controls 540) Replication Panel 1,196	Illumina ~550,000	4	Wang et al. [47] Hindorff et al. [34]
GWAS of obesity	Initial Panel 327 (Cases 164, Controls 163) Replication Panel 10,337 (Cases 4,674, Controls 5,663)	Affymetrix 406,177	2	Jiao et al. [48] Hindorff et al. [34]
GWAS of body mass index	Initial Panel 1,715 Replication Panel 3,274	Affymetrix 746,626	2	Ng et al. [49] Hindorff et al. [34]
GWAS of body mass index	Initial Panel 123,865 Replication Panel 125,931	Affymetrix, Illumina and Perlegen ~2.8 million (imputed)	38	Speliotes et al. [50] Hindorff et al. [34]
Meta-analysis of extreme obesity	Initial Panel 2,258 Replication Panel A 5,829 Replication Panel B 31,182	Affymetrix & Illumina 1,596,878 (imputed)	5	Scherag et al. [51] Hindorff et al. [34]
GWAS of adult body mass index in a British population	9,377	Affymetrix GeneChip Mapping 500K Illumina Infinium HumanHap550	528,865	Strachan et al. [52]
GWAS of obesity	10,391	Illumina 1,283,957 (imputed)	1	Dorajoo et al. [53] Hindorff et al. [34]
Meta-analysis of GWAS informative for adult waist circumference and waist- hip ratio	Initial Panel 38,580 Replication Panel 102,064	Affymetrix and Illumina 2,573,738 (imputed)	3	Lindgren et al. [54] Hindorff et al. [34]

Table 1: List of GWAS and meta-analysis for initial data set.

Results and Discussion

The five different analysis results are shown in Tables 2 to 7 and the same results are depicted in Figure 1. The positional integration approach yielded a prioritized list of genomic region, where the regions containing the highest accumulation of diverse biological alterations in obesity rank highest. We identified 49 high scoring gene regions (Tables 2 and 3) with the doubled input of genomic data and the normal weighed transcriptomic, proteomic, microRNA level and epigenetic. The transcriptomic data weighed double resulted in 132 high scoring genes (Table 4). Table 5 depicts 40 high scoring gene regions for the double weighed proteomic data and the normal weighed genomic, transcriptomic, microRNA level and epigenetic data. Table 6 depicts 63 high scoring gene regions for the double weighed microRNA. The double weighed epigenetic with the single weighed other data sources showed 24 high scoring gene regions (Table 7).

We selected ten gene regions that were exhibiting the highest scores and found in more than one analysis results (ATP5O, ALK7, GADPH, IFFO1, NCAPD2, DDX50, MAOB, ATM, STOX1 and PRRC2A). In a prior study the eight highest scoring gene regions (ATP5O, ALK7, CR1, CR2, S100, GAPDH, TLR1 and TLR6) were discussed for their association to obesity. Since ATP5O, ALK7 and GADPH were among the previously discussed gene regions, the results of the second analysis prove to be consistent with our first study [32].

All of the remaining 7 identified gene regions (IFFO1, NCAPD2, DDX50, MAOB, ATM, STOX1 and PRRC2A) were also identified in our prior study [32], however, the gene regions were not discussed as they where not identified to be highest scoring regions but can be identified in the supplementary data.

The two genes that were found in all high scoring tables were ATP5O and ACVR1C or ALK7. GAPDH, IFFO1 and NCAPD2 were

Identification No.	Title	Number of Individuals	Analytical Method	Refernce
GSE20950	Morbidly obese insulin-resistant patients: omental and subcutaneous adipose tissue	10	Affymetrix Human Genome U133 Plus 2.0 Array & real time PCR	Hardy, Perugini, Nicoloro, Gallagher-Dorval et al. [55]
GSE27951	Adipogenesis and obesity: subcutaneous adipose tissue (HG-U133_Plus_2)	20	Affymetrix Human Genome U133 Plus 2.0 Array	Keller, Gburcik, Petrovic, Gallagher et al. [56]
GSE15524	Morbid obesity: subcutaneous and omental adipose tissues	11	CodeLink UniSet Human 20K I Bioarray	MacLaren, Cui, Lu, Simard et al. [57]
GSE474	Obesity and fatty acid oxidation	16	Affymetrix Human Genome U133A Array	Park, Berggren, Hulver, Houmard et al. [58]
GSE15773	Obesity-associated insulin resistance independent of BMI: omental and subcutaneous adipose tissues	20	Affymetrix Human Genome U133 Plus 2.0 Array	Hardy, Perugini, Nicoloro, Gallagher-Dorval et al. [55]
GSE15653	Obese patients with and without type 2 diabetes: liver	18 (Cases 13, Controls 5)	Affymetrix Human Genome U133A Array	Pihlajamäki, Boes, Kim, Dearie et al. [59]
GSE22435	Expression of Splicing Factor Genes is Reduced in Human Obesity and Contributes to Enhanced Lipogenesis	17 (Cases 7, Controls 10)	Affymetrix Human Genome U133 Plus 2.0 Array	Pihlajamäki, Lerin, Itkonen, Boes et al. [60]
GSE25401	Adipose Tissue MicroRNAs as Regulators of CCL2 Production in Human Obesity [gene expression]	56 (Cases 30, Conroles 26)	Affymetrix Human Gene 1.0 ST Array	Arner, Mejhert, Kulyté, Balwierz et al. [61]
GSE25402	Adipose Tissue MicroRNAs as Regulators of CCL2 Production in Human Obesity	56	Affymetrix Human Gene 1.0 ST Array [transcript (gene) version]	Arner, Mejhert, Kulyté, Balwierz et al. [61]
GSE24883	Worsening of Obesity and Metabolic Status Yields Similar Molecular Adaptations_ Subcutaneous and Visceral Adipose Tissue	32	Agilent-014850 Whole Human Genome Microarray 4x44K G4112F (Feature Number version)	Klimcáková, Roussel, Márquez-Quiñones, Kovácová et al. [62]

Table 2: List of transcriptomic data for initial data set.

detected over all analysis results with the exception of the epigenetic level. The genes DDX50 and MAOB show high ranks in the double weighed transcriptomic- and the microRNA analysis results. ATM and STOX1 were identified by the transcriptomic data and the proteomic data. PRRC2A was found in the genomic- and transcriptomic results.

ATP5O was the most reduced OXPHOS gene in an expression profile in skeletal muscle from patients with T2D in comparison with healthy control subjects [68]. Ronn et al. [69] conducted a twin study, which showed that genetic variations in the ATP5O gene region is associated with mRNA expression in skeletal muscle and glucose increase in young twins. It was shown in a number of respective studies that aging had a negative effect on ATP5O mRNA expression, which also agrees with findings for other OXPHOS genes [70-72]. These findings suggest combinations of genetic and non-genetic factors may shape the reduced expression of ATP5O in obesity-associated T2DM [68], which concurs with our performed integration study [32].

It has been demonstrated that Activin receptor-like kinase 7 (ALK7) is expressed in pancreatic islets and beta-cell lines [73]. In a study by Watanabe et al. [74] it was noticed, that the human insulin promoter was activated in the ALK7 pathway by Smad2, Smad3 and homeobox factor-1 (PDX-1) of pancreas and duodenum. The study results show that one of the direct target genes of Nodal and Activin

Gene Name	Chromosome Name	Region start	Region stop	Score
ACVR1C	chr2	1.58E+08	1.59E+08	6.1
MIR190B	chr1	1.54E+08	1.54E+08	6.1
ATP5O	chr21	35275000	35324999	5.2
PTK2	chr8	1.42E+08	1.42E+08	5.2
GULP1	chr2	1.89E+08	1.89E+08	4.6
MCCC1	chr3	1.83E+08	1.83E+08	4.6
TRIM13	chr13	50575000	50624999	4.6
ATF2	chr2	1.76E+08	1.76E+08	4.4
ATP5G3	chr2	1.76E+08	1.76E+08	4.4
MIR933	chr2	1.76E+08	1.76E+08	4.4
PDIA5	chr3	1.23E+08	1.23E+08	4.4
SEC22A	chr3	1.23E+08	1.23E+08	4.4
CA6	chr1	9000000	9049999	4.3
PTH2R	chr2	2.09E+08	2.09E+08	4.3
ACACB	chr12	1.1E+08	1.1E+08	4.2
ANXA3	chr4	79525000	79574999	4.2
GAPDH	chr12	6625000	6674999	4.2
IFFO1	chr12	6625000	6674999	4.2
MYO5A	chr15	52575000	52624999	4.2
MYO5C	chr15	52575000	52624999	4.2
NCAPD2	chr12	6625000	6674999	4.2
BACH2	chr6	90900000	90949999	4.1
CPNE4	chr3	1.31E+08	1.32E+08	4.1
LMBR1L	chr12	49500000	49549999	4.1
TUBA1B	chr12	49500000	49549999	4.1
CYP39A1	chr6	46600000	46649999	4
DMD	chrX	31325000	31374999	4
DMD-AS2	chrX	31325000	31374999	4
SLC25A27	chr6	46600000	46649999	4
AASS	chr7	1.22E+08	1.22E+08	3.9
ANKRD32	chr5	94025000	94074999	3.9
BIRC2	chr11	1.02E+08	1.02E+08	3.9
BIRC3	chr11	1.02E+08	1.02E+08	3.9
FAM13B	chr5	1.37E+08	1.37E+08	3.9
FGF2	chr4	1.24E+08	1.24E+08	3.9
MCTP1	chr5	94025000	94074999	3.9
AIF1	chr6	31575000	31624999	3.8
DAPK2	chr15	64200000	64249999	3.8
PANX1	chr11	93875000	93924999	3.8
PRRC2A	chr6	31575000	31624999	3.8
SNORA38	chr6	31575000	31624999	3.8
UQCRHP1	chr6	31575000	31624999	3.8

Table 3: Results genomic and all data (2:1).

Gene Name	Chromosome Name	Region start	Region stop	Score
ATP5O	chr21	35275000	35324999	7.1
ACVR1C	chr2	1.58E+08	1.59E+08	6.8
GAPDH	chr12	6625000	6674999	6.2
IFFO1	chr12	6625000	6674999	6.2
NCAPD2	chr12	6625000	6674999	6.2
ETV6	chr12	11800000	12074999	5.8
HADH	chr4	1.09E+08	1.09E+08	5.8
TXNL1	chr18	54275000	54349999	5.3
ATM	chr11	1.08E+08	1.08E+08	5.2
NPAT	chr11	1.08E+08	1.08E+08	5.2
ATP8A1	chr4	42400000	42449999	4.9
FAU	chr11	64875000	64924999	4.9
PKD2	chr4	88925000	89024999	4.9
SHISA3	chr4	42400000	42449999	4.9
SYVN1	chr11	64875000	64924999	4.9
TM7SF2	chr11	64875000	64924999	4.9
VPS51	chr11	64875000	64924999	4.9
WDR7	chr18	54300000	54349999	4.9
GLULP4	chr9	34900000	34949999	4.8
YWHAZP6	chr9	34900000	34949999	4.8
ZNHIT2	chr11	64875000	64924999	4.8
AIF1	chr6	31575000	31624999	4.7
PRRC2A	chr6	31575000	31624999	4.7
SNORA38	chr6	31575000	31624999	4.7
UQCRHP1	chr6	31575000	31624999	4.7
CHTOP	chr1	1.54E+08	1.54E+08	4.6
LEF1	chr4	1.09E+08	1.09E+08	4.6
S100A1	chr1	1.54E+08	1.54E+08	4.6
ARID3C	chr9	34625000	34674999	4.1
DCN	chr12	91550000	91599999	4.1
EGFL6	chrX	13575000	13674999	4.1
F11	chr4	1.87E+08	1.87E+08	4.1
GALT	chr9	34625000	34674999	4.1
GATAD2A	chr19	19525000	19574999	4.1
IRS2	chr13	1.1E+08	1.1E+08	4.1
KLKB1	chr4	1.87E+08	1.87E+08	4.1
MASP2	chr1	11075000	11124999	4.1
MIR640	chr19	19525000	19574999	4.1
MYO5A	chr15	52575000	52624999	4.1
MYO5C	chr15	52575000	52624999	4.1
RPL30P15	chrX	13575000	13624999	4.1
SIGMAR1	chr9	34625000	34674999	4.1
TARDBP	chr1	11075000	11124999	4.1
ADORA1	chr1	2.03E+08	2.03E+08	4
AGPAT5	chr8	6600000	6649999	4
ANG	chr14	21150000	21199999	4
ATP6V1B1	chr2	71150000	71199999	4
BLOC1S1	chr12	56100000	56149999	4
CD63	chr12	56100000	56149999	4
CRLS1	chr20	5975000	6024999	4
DIMT1	chr5	61675000	61724999	4
FAM102B	chr1	1.09E+08	1.09E+08	4
INF2	chr14	1.05E+08	1.05E+08	4
IPO11	chr5	61675000	61724999	4
ITGA7	chr12	56100000	56149999	4
KIF2A	chr5	61675000	61724999	4
MCM8	chr20	5975000	6024999	4
MIR4659A	chr8	6600000	6649999	4
MIR4659B	chr8	6600000	6649999	4
MYOG	chr1	2.03E+08	2.03E+08	4
MYOZ3	chr5	1.5E+08	1.5E+08	4
PDIA5	chr3	1.23E+08	1.23E+08	4
RAD23B	chr9	1.1E+08	1.1E+08	4
RDH5	chr12	56100000	56149999	4
RNASE4	chr14	21150000	21199999	4
SEC22A	chr3	1.23E+08	1.23E+08	4
SLC24A6	chr12	1.14E+08	1.14E+08	4
SLC8A1	chr2	40475000	40524999	4
SLC8A1-AS1	chr2	40475000	40524999	4
SYNPO	chr5	1.5E+08	1.5E+08	4
TNMD	chrX	99825000	99899999	4
TPCN1	chr12	1.14E+08	1.14E+08	4
VAX2	chr2	71150000	71199999	4
ADAM9	chr8	38850000	38899999	3.9
BMP2K	chr4	79750000	79799999	3.9
ERGIC2	chr12	29475000	29524999	3.9
FAR2	chr12	29475000	29524999	3.9
FGF2	chr4	1.24E+08	1.24E+08	3.9
GLUL	chr1	1.82E+08	1.82E+08	3.9
LSAMP	chr3	1.16E+08	1.16E+08	3.9
MAOB	chrX	43675000	43724999	3.9
MIR208B	chr14	23875000	23924999	3.9
MYH6	chr14	23875000	23924999	3.9
MYH7	chr14	23875000	23924999	3.9
NFAT5	chr16	69725000	69774999	3.9
NQO1	chr16	69725000	69774999	3.9
OSBPL11	chr3	1.25E+08	1.25E+08	3.9
PYGM	chr11	64500000	64549999	3.9
RASGRP2	chr11	64500000	64549999	3.9
RNASEH1	chr2	3600000	3649999	3.9
RPS7	chr2	3600000	3649999	3.9
SNX4	chr3	1.25E+08	1.25E+08	3.9
TM2D2	chr8	38850000	38899999	3.9
CR1	chr1	2.08E+08	2.08E+08	3.8
DUSP14	chr17	35850000	35899999	3.8
PALLD	chr4	1.7E+08	1.7E+08	3.8
SC5DL	chr11	1.21E+08	1.21E+08	3.8
SEC61A2	chr10	12175000	12224999	3.8
SYNRG	chr17	35850000	35899999	3.8
TEDDM1	chr1	1.82E+08	1.82E+08	3.8
ADH1B	chr4	1E+08	1E+08	4.1

Table 4: Results transcriptomic and all data (2:1).

AB signals is the insulin gene in pancreatic beta-cells and that PDX-1 is immediately connected with the ALK7-Smad pathway [74-76].

Prior GADPH was disputed to be involved in neurodegenerative diseases [77] and different types of cancers [78]. Hwang et al. [79] study acknowledges that an important oxidative target of ROS is GAPDH. One of the consequences of oxidative stress is a decrease in cellular ATP levels and blocked glycolysis [80,81], due to the inactivation of the glycolytic enzyme GAPDH.

The gene IFFO1 is a member of the intermediate filament family. Intermediate filaments are proteins which are original components of the cytoskeleton. The members of this gene family are evolutionarily

Gene Name	Chromosome Name	Region start	Region stop	Score
RAP2B	chr3	1.53E+08	1.53E+08	5.2
ACVR1C	chr2	1.58E+08	1.58E+08	5
ETV6	chr12	11800000	11849999	4.9
ATP6V1B1	chr2	71150000	71199999	4.8
VAX2	chr2	71150000	71199999	4.8
E2F4	chr16	67225000	67274999	4.7
ELMO3	chr16	67225000	67274999	4.7
LRRC29	chr16	67225000	67274999	4.7
MIR328	chr16	67225000	67274999	4.7
TNMD	chrX	99850000	99899999	4.7
EEF1A2	chr20	62100000	62149999	4.6
KCNQ2	chr20	62100000	62149999	4.6
NDUFAF1	chr15	41675000	41724999	4.6
ATP5O	chr21	35275000	35324999	4.5
HOXB-AS4	chr17	46700000	46749999	4.5
HOXB9	chr17	46700000	46749999	4.5
MIR151A	chr8	1.42E+08	1.42E+08	4.5
MIR196A1	chr17	46700000	46749999	4.5
PHEX	chrX	22075000	22124999	4.5
PTK2	chr8	1.42E+08	1.42E+08	4.5
GAPDH	chr12	6625000	6674999	4.3
IFFO1	chr12	6625000	6674999	4.3
NCAPD2	chr12	6625000	6674999	4.3
ACSS3	chr12	81475000	81524999	4.2
ATM	chr11	1.08E+08	1.08E+08	4.2
C11orf65	chr11	1.08E+08	1.08E+08	4.2
C1orf189	chr1	1.54E+08	1.54E+08	4.2
MFAP3	chr5	1.53E+08	1.53E+08	4.2
MIR190B	chr1	1.54E+08	1.54E+08	4.2
MIR378A	chr5	1.49E+08	1.49E+08	4.2
PPARGC1B	chr5	1.49E+08	1.49E+08	4.2
TPM3	chr1	1.54E+08	1.54E+08	4.2
ADAM9	chr8	38875000	38924999	4.1
COL14A1	chr8	1.21E+08	1.21E+08	4.1
G3BP1	chr5	1.51E+08	1.51E+08	4.1
HEYL	chr1	40100000	40149999	4
NT5C1A	chr1	40100000	40149999	4
CHTOP	chr1	1.54E+08	1.54E+08	3.9
GPATCH2	chr1	2.18E+08	2.18E+08	3.9
HNRNPA1	chr12	54675000	54724999	3.9
MIR143	chr5	1.49E+08	1.49E+08	3.9
MIR143HG	chr5	1.49E+08	1.49E+08	3.9
MIR145	chr5	1.49E+08	1.49E+08	3.9
S100A1	chr1	1.54E+08	1.54E+08	3.9
S100A13	chr1	1.54E+08	1.54E+08	3.9
SNORD12	chr20	47875000	47924999	3.9
SNORD12B	chr20	47875000	47924999	3.9
SNORD12C	chr20	47875000	47924999	3.9
SPATA17	chr1	2.18E+08	2.18E+08	3.9
YWHAZP6	chr9	34900000	34949999	3.9
ZNFX1	chr20	47875000	47924999	3.9
ZNFX1-AS1	chr20	47875000	47924999	3.9
ABCF1	chr6	30550000	30599999	3.8
ABCF1	chr6	30550000	30599999	3.8
COPZ1	chr12	54675000	54724999	3.8
EPS15	chr1	51975000	52024999	3.8
GLULP4	chr9	34900000	34949999	3.8
IARS2	chr1	2.2E+08	2.2E+08	3.8
MIR194-1	chr1	2.2E+08	2.2E+08	3.8
MIR215	chr1	2.2E+08	2.2E+08	3.8
MIR877	chr6	30550000	30599999	3.8
NFE2	chr12	54675000	54724999	3.8
PPP1R10	chr6	30550000	30599999	3.8

Table 5: Results proteomic and all data (2:1).

Gene Name	Chromosome Name	Region start	Region stop	Score
ATP5O	chr21	35275000	35324999	6.1
CDCP1	chr3	45175000	45224999	5.3
GAPDH	chr12	6625000	6674999	5.3
IFFO1	chr12	6625000	6674999	5.3
NCAPD2	chr12	6625000	6674999	5.3
RAB21	chr12	72175000	72224999	5.3
BTK	chrX	100625000	1.01E+08	5.2
RPL36A	chrX	100625000	1.01E+08	5.2
GATAD2A	chr19	19525000	19574999	5
MIR640	chr19	19525000	19574999	5
OXSR1	chr3	38250000	38299999	5
ADH1B	chr4	100225000	1E+08	4.9
CD99	chrX	2600000	2649999	4.7
EYA4	chr6	133700000	1.34E+08	4.7
FAM227B	chr15	49725000	49774999	4.7
FGF7	chr15	49725000	49774999	4.7
SOX5	chr12	24075000	24124999	4.7
ACVR1C	chr2	158425000	1.58E+08	4.6
ABCC1	chr16	16225000	16274999	4.4
ABCC6	chr16	16225000	16274999	4.4
ANGPT1	chr8	108275000	1.08E+08	4.4
MAOB	chrX	43675000	43724999	4.4
PFKFB4	chr3	48575000	48624999	4.4
UCN2	chr3	48575000	48624999	4.4
PDE4DIP	chr1	144950000	1.45E+08	4.2
VBP1	chrX	154450000	1.54E+08	4.2
DDX50	chr10	70650000	70699999	4.1
FAM49B	chr8	130950000	1.31E+08	4.1
LRP1B	chr2	141800000	1.42E+08	4.1
RELN	chr7	103575000	1.04E+08	4.1
STOX1	chr10	70650000	70699999	4.1
C8orf74	chr8	10525000	10574999	3.9
CHST15	chr10	125850000	1.26E+08	3.9
CYB561	chr17	61500000	61549999	3.9
PRICKLE2	chr3	64200000	64249999	3.9
RNA5SP25	chr8	10525000	10574999	3.9
2				
RP1L1	chr8	10525000	10574999	3.9
TANC2	chr17	61500000	61549999	3.9
RPL37A	chr2	217350000	2.17E+08	3.8
SCMH1	chr1	41600000	41649999	3.8

Table 6: Results microRNA and all data (2:1).

and structurally related but the proteins encoded have limited sequence homology, with the exception of the central rod domain. There have been multiple alternatively spliced transcript variants encoding different isoforms found [82]. For example, a protein interaction

Gene Name	Chromosome	Region start	Region stop	Score
NDUFAF1	chr15	41675000	41724999	5.6
PTPRJ	chr11	48150000	48199999	4.8
ATP5O	chr21	35275000	35324999	4.5
ACVR1C	chr2	1.58E+08	1.58E+08	4.4
KIAA1467	chr12	13200000	13249999	4.4
MAP3K5	chr6	1.37E+08	1.37E+08	4.4
PPP2R3A	chr3	1.36E+08	1.36E+08	4.4
C11orf63	chr11	1.23E+08	1.23E+08	4.2
FAM13A	chr4	89700000	89749999	4
GPD1L	chr3	32150000	32199999	4
PBLD	chr10	70025000	70074999	4
RAD23B	chr9	1.1E+08	1.1E+08	4
RGS7	chr1	2.41E+08	2.41E+08	4
SNTG1	chr8	51350000	51399999	4
BAI3	chr6	69875000	69924999	3.9
BMP2K	chr4	79825000	79874999	3.9
C12orf52	chr12	1.14E+08	1.14E+08	3.9
C16orf74	chr16	85725000	85774999	3.9
IQCD	chr12	1.14E+08	1.14E+08	3.9
LSAMP	chr3	1.16E+08	1.16E+08	3.9
PAQR3	chr4	79825000	79874999	3.9
SLC8A1	chr2	40450000	40499999	3.9
SLC8A1-	chr2	40450000	40499999	3.9
AS1				
DTNA	chr18	32350000	32399999	3.8

Table 7: Results epigenetic and all data (2:1).

network of alternatively spliced isoforms from brain connects genetic risk factors for autism or neurodegenerative disorders [83].

Non-SMC condensin I complex, subunit D2 (NCAPD2, also known as CNAP1) demonstrated to be one of the two SNPs located in two adjacent genes that was demonstrated to be nominally significant association with Alzheimer's Disease. Interestingly, the other adjacent gene identified was GAPDH [84].

In general, the DEAD box proteins are described by a motif of proteins Asp-Glu-Ala-Asp (DEAD). They are putative RNA helicases. DDX50 is involved in a number of cellular processes including the change of RNA secondary structure such as nuclear and mitochondrial splicing, translation initiation and ribosome and spliceosome construction. On the basis of their distribution, some members of this DEAD box protein family are believed to be involved in embryogenesis, cellular growth and division and spermatogenesis [85].

Monoamine oxidase (MAO) appears in two functional forms: MAO-A and MAO-B. The genes of both protein isoforms exhibits identical exon–intron organization, but have different substrate and inhibitor specificities and are encoded by separate genes that are located tail-to-tail on the X chromosome. While MAO-A removes serotonine, norepinephrine and is selectively inhibited by clorgyline, the MAO-B is more efficient in degrading phenylethylamine and benzylamine and is selectively inhibited by deprenyl [86,87]. Both enzymes are exhibited in various tissues throughout the body with the highest levels of expression in liver. Increased levels of MAO-B mRNA and enzymatic activity have been observed in platelets from patients with Parkinson's and Alzheimer's diseases, however the triggers of enhanced mRNA levels are unknown [88].

ATM was identified in two of our analysis as high scoring gene region. It harbors a SNP (rs11212617) and is located within a large block of linkage disequilibrium that includes also the genes CUL5, C11orf65, ACAT1, NPAT, KDELC2, EXPH5. Ataxia Telangiectasia (A-T) or the Louis Bar Syndrome is caused by a homozygous loss of function mutations in ATM. A-T is a neurodegenerative disorder which is described by loss of muscle coordination and progressive ataxia, immunodeficiency, radio sensitivity and a predisposition to cancer [89]. Also, patients with A-T have been shown to have noticeable insulin resistance and increased risk of diabetes [90,91]. Further, previous reports indicate that inhibition or activation of ATM changes AMPK activation [92-94]. Not one of the other genes have been identified to be associated with diabetes or insulin action at the locus. In the study by Zhou et al. [95] the association of ATM in the glycaemic response to metformin establishes another connection between cancer pathways, T2DM and metformin activation of AMPK.

The high scoring gene STOX1 was exhibited in the analysis results of the double weighed transcriptomic- and proteomic data. Many functions as a DNA binding protein is encoded by this gene. Alterations in this gene are connected with pre-eclampsia/eclampsia 4 (PEE4) and might be also linked to the late on set of Alzheimer's Disease [96].

PRRC2A (Proline-rich and coiled-coil-containing protein 2A) also known as BAT2 has been localized adjacent to genes for TNF alpha and TNF beta. The gene is located within the human major histocompatibility complex class III region. It has microsatellite repeats which are connected with the age-at-onset of insulin-dependent diabetes mellitus and possibly associated with the inflammatory process of pancreatic beta-cell degeneration, which occurs during the establishment of insulin-dependent diabetes mellitus. Also this gene is a candidate gene for the development of rheumatoid arthritis [97].

Even though the identified gene regions could not be linked directly to obesity, 8 of 9 discussed genes were associated either to T2DM or a type of neurodegenerative disease. Several epidemiological studies have indicated that being obese increases the risk of neurodegenerative diseases [98-102] and T2DM. The underlying mechanisms of the association among obesity, T2DM and neurodegenerative diseases are not precisely defined, but some mechanistic insight can be inferred. For example, obesity has been associated with several processes related to the acceleration of aging, including the excessive production of free radicals, oxidation and inflammation [103-106]. In addition, a link between obesity-related complications and neurodegenerative disease have been noted by epidemiological research, [107]. Other studies indicate a link between T2DM and fatty liver disease (NAFLD), the hepatic manifestation of metabolic syndrome [108], with Alzheimer`s disease [109]. T2DM patients have twice the occurrence of sporadic Alzheimer`s disease than their non-diabetic controls [110,111]. NAFLD is characterized by hepatic triglyceride accumulation without excessive alcohol intake that may lead to cirrhosis and is also associated with raised risks of cardiovascular events and T2DM development [112,113]. Reports note that up to 50% of NAFLD patients may experience mild cognitive impairment [114]. NAFLD pathophysiology is complex, but insulin resistance has a central role in its development and is therefore closely linked to metabolic syndrome and T2DM [115,116]. One pathway that is related to cancer, Alzheimer`s disease, autism, schizophrenia, Parkinson, NAFLD and fibrosis is the Wnt signaling pathway, which regulates functions like cell proliferation, polarity, apoptosis, inflammation and differentiation in almost all tissues, including the liver, muscle, kidney and brain [117].

The results of our integration of different OMICs layers indicate

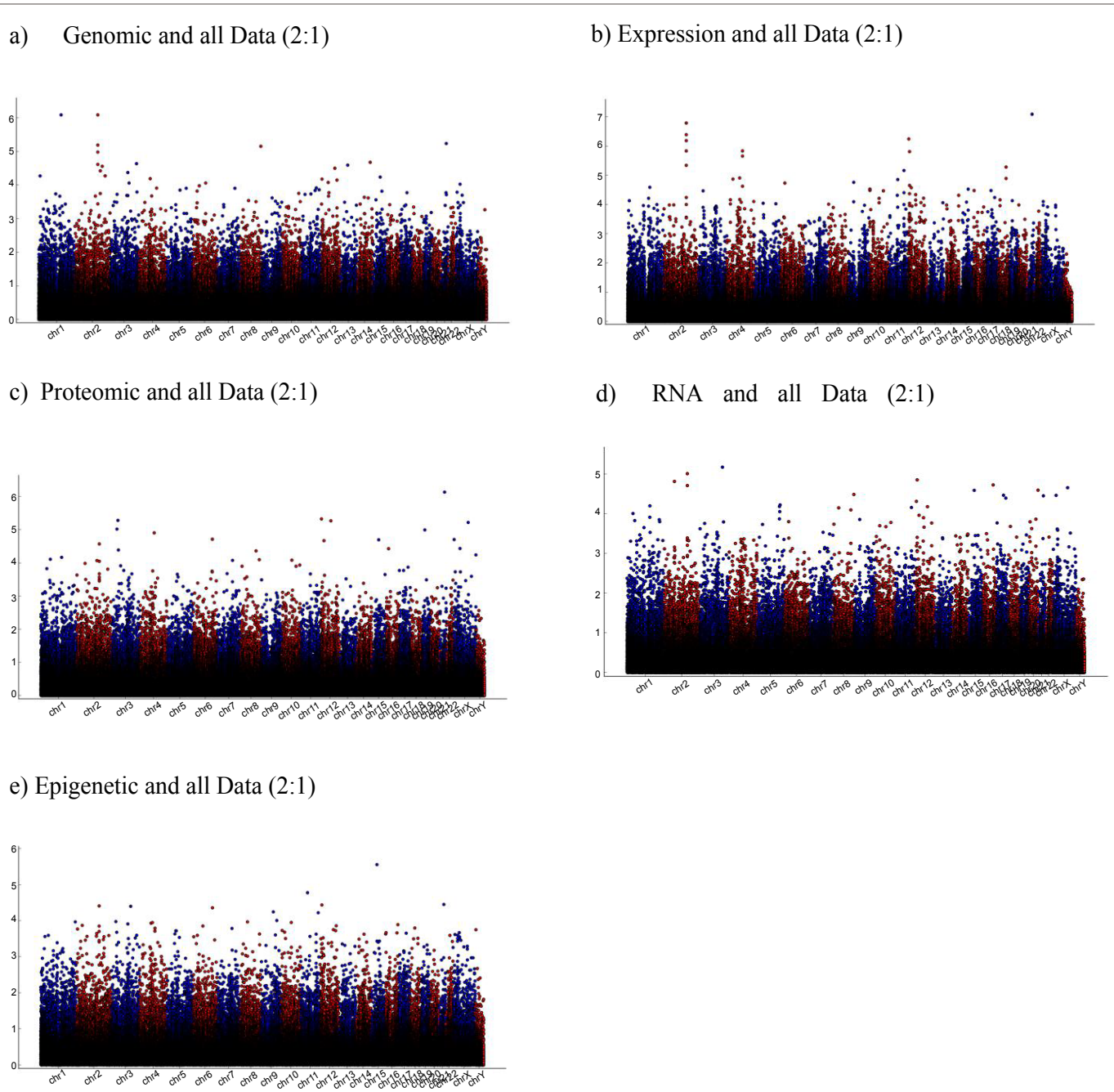

Figure 1: High scoring gene regions. a-e) gives a first impression of our high scoring gene regions. A genome-wide plot displays the distribution of calculated P-values across the genome. X-axis represents locations of the region on genomic backbone and Y-axis represents −log10p estimates of P-values obtained permutation.

potential new gene regions of interest for obesity research, with are in close relation to different types of neurodegenerative disorders.

In our prior study we discussed and pointed out the pros and cons of the position-centric integration approach, we mentioned the choice of region size used for integration, which may result in difficulties by choosing a region too small important long-range interactions may be missed, while choosing a larger region a high amount of false positive genes may be found [32].

Through the weighing of the data we verified on one hand the tool and the consistency of the product data. It shows that the results and the assessed data itself is consistent on all data levels. However, we have to point out that without the data weighing we would have not discovered which gene regions where identified in all or in multiple approaches that highlight one OMICs level.

Conclusion

In this study, we applied a new method of positional integrational analysis of different OMIC-layers and a validation step, where we weighed the initial data to confirm prior findings and identify new targets for obesity research. Even though, the ten high ranked and discussed genes could not be directly linked to obesity nine of them

are associated with T2DM and neurodegenerative disease. Both disorders show a higher prevalence in obese individuals compared to lean. Thus our study provides a basis for further research to elucidate underlying mechanisms of these associations and identify new targets for preventive and therapeutic interventions.

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