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COP 5859
Take Home Midterm Part 1
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Part 1 of Midterm: Obesity

Abstract:

The paper "Genetics of Obesity" is a thorough exploration into the genetics of obesity, covering many different angles and definitions of obesity. To summarize the organization of the paper: it begins by explaining the high degree of heritability of obesity, then explaining the shortcomings of previous methods, namely linkage studies, in identifying the genetics behind the heritability, and finally going into deep detail describing the reasons GWAS is appropriate for studying obesity and the results of relevant association studies. This report aims to analyze this paper, and expand upon the genes identified from the cited GWA studies by conducting GO term enrichment. We will do so by compiling lists of relevant genes and gene products from related papers and delving into the biological pathways and molecular functions they affect ultimately causing obesity.

Background:

The first step the paper takes is in establishing that obesity is, in fact, highly heritable, meaning that there exist powerful genetic components contributing to it. According to them, various twin studies, from identical twins being raised apart to monozygotic twin studies in controlled experiments of caloric intake, give strong evidence of a high heritability for obesity and obesity-related traits such as body mass index. The estimates of heritability across various studies puts the figures at 0.47 to 0.90 in twin studies and 0.24 to 0.81 for family studies, both of which are significant even on the lower ends. The earliest attempts at exploring the genetic bases of this high heritability were linkage studies, which fell short of accomplishing their goal and were later replaced largely by association studies of obesity.

Linkage studies and association studies are flip sides of the same coin, as they go in opposite directions. In a linkage study, you have a trait in question that you are trying to explore, usually a disease, and to discover the trait's genetic links you look at the individuals expressing the phenotype of this trait and other closely-related individuals, such as family members. If afflicted individuals in the family, in the case of this report being those who are obese, all share common genetic mutations, while those not

afflicted do not share these mutations, a linkage study will have discovered a genetic basis for obesity. Association studies, on the other hand, look first at the genomes across large populations, not just pedigrees of relatively small size as in linkage studies, and then look to see if there are statistically significant expressions of phenotypes associated with specific genes.

The reason linkage studies were unsuitable for investigating obesity was because obesity was found to not be controlled by highly penetrant variants of specific alleles. Linkage studies are suitable for cases with rare diseases within small groups of related individuals, where the trait is attributable to one or a few changes in the genome that are highly causal for that phenotype.

Association studies, as stated in the previous paragraph, first look at candidate genes found by biological analysis that selects genes as being potentially related to the phenotype in question. They then ask the question of whether the genes are statistically related to the trait by looking at the genomes of large populations and comparing the variants of these genes with the observed phenotypes. Several important genes for obesity were found this way, such as MC4R, which is associated with severe, early-onset obesity. However, while association studies discovered a few genes, genome-wide association studies have been the biggest contributor to discovering obesity-associated genes and variants.

Genome-wide association studies (GWAS) are an expansion on association studies. Unlike in standard association studies, where specific candidate genes are selected and checked to see if they correlate with the phenotype being studied, in a GWAS there is no pre-selection of candidate genes. The information fed into a GWAS is one population expressing the phenotype being studied and one population of controls, along with the corresponding genotypes. A typical GWAS will find associations between the afflicted population, usually in the form of single nucleotide polymorphisms (SNP). The genes that these SNPs exist on are assigned p-values for significance, and the output of the GWAS is a list of these genes with their significance values. Thus, it is up to the researcher after a GWAS to analyze the genes to see what their mechanisms are for causing the phenotype being studied.

The benefit of GWAS is in gene discovery, especially for a trait such as obesity that has many contributing factors. With this knowledge, we will gather the already known obesity-related genes from the paper on pre-GWAS genetics titled “Genetic Variation and Obesity Prior to the Era of Genome-Wide

Association Studies." Then, we will compile a list on post-GWAS obesity genetics from the paper "Genome-Wide Association Studies of Obesity" and use these lists together for enrichment analysis.

Methods:

The first thing we did was collect all the genes from the pre-GWAS paper:

Name	HGNC Symbol
Leptin	LEP
Leptin Receptor	LEPR
MC4R	MC4R
POMC	OBAIRH
PCSK1	PCSK1
SNRPN	PWS
	SNRPN
	NDN
	BBS1
Alms1	ALMS
AGRP	AGRP
BDNF	BDNF
Sybecans	SDC1
	SDC3
Sim1	SIM1
CART	CARTPT
Directing Energy	UCP1
	UCP3
GHRL	GHRL
GHSR	GHSR
PYY	PYY
PPAR	PPARG
PPARGC1B	PPARGC1B
NROB2	NROB2
ENPP1	ENPP1
ADRB	ADRB2
	ADRB3

Figure 1. Pre-GWAS Genes List

Then, we gathered genes and gene products to form a lists from the paper “Genetics of Obesity” and post-GWAS paper:

INSIG2	FAIM2	GP2
FTO	FANCL	KCNMA1
MC4R	FLJ35779	NPC1
GNPDA2	GIPR	PTER
KCTD15	GNPDA2	HS6ST3
MTCH2	GRPC5B	MAF
NEGR1	LRRN6C	NPC1
SH2B1	MC4R	PTER
TMEM18	NEGR1	KCNMA1
BDNF	SEC16B	SDCCAG8
ETV5	SH2B1	GNAT2
SEC16B	TFAP2B	HNF4G
ADCY3-POMC	TMEM18	MRPS33P4
CADM2	HS6ST3	HNF4G
KCTD15	KCNMA	TNKS/MSRA
LRP1B	LEPR	IRS1
MAP2K5	MAF	SPRY2
MTCH2	OLFM4	FTM
MTIF3	PACS1	RPGRIP1L
NRXN3	PRKCH	MC4R
NUDT3	RMST	SH2B1
PRKD1	TNKS/MSRA	GIPR
PTBP2	ZZZ3	TMEM160-ZC3H4
RPL27A	ADAMTS9	LYPLAL1
SLC39A8	CPEB4	AA553656
TMEM160	DNM3-PIGC	GRB14
TNNI3K	GRB14	PIGC
ZNF608	HOXC13	STAB1
RSPO3	ITPR2-SSPN	TBX15
TBX15-WARS2	LY86	ZNRF3
PCSK1	LYPLAL1	NISCH-STAB1
CDKAL1	NFE2L3	KLF9

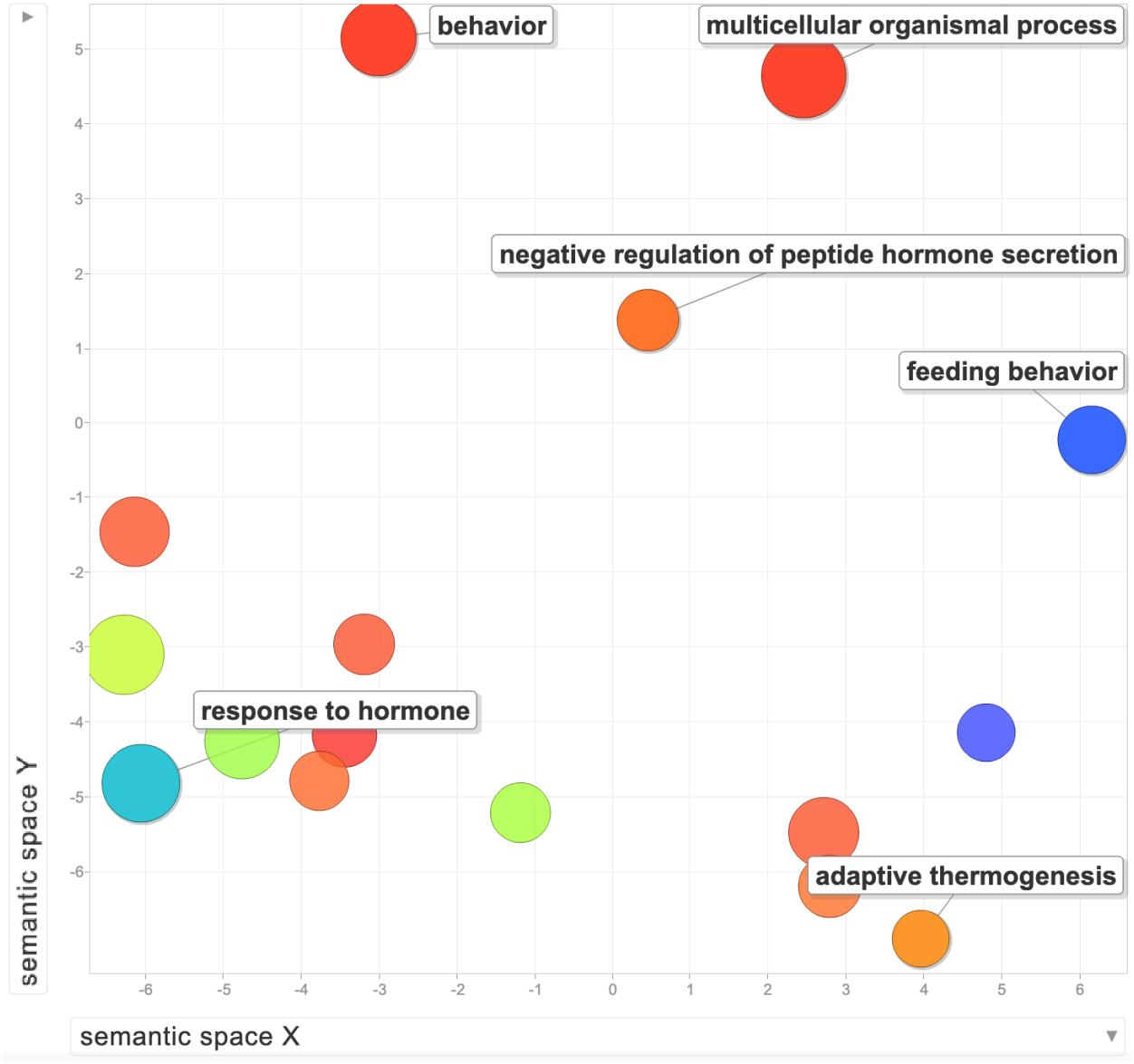
Figure 2. Post-GWAS Genes List

We then combined the pre-GWAS and post-GWAS lists and did enrichment analysis with the Gene Ontology tool to observe differences arising from GWAS genes.

Results:

GO Biological Process	GO Term ID	P-value
adult feeding behavior	GO:0008343	2.15E-05
feeding behavior	GO:0007631	3.05E-05
response to hormone	GO:0009725	1.16E-04
response to nutrient levels	GO:0031667	7.24E-04
response to dietary excess	GO:0002021	8.12E-04
cellular response to hormone stimulus	GO:0032870	9.78E-04
response to endogenous stimulus	GO:0009719	1.18E-03
regulation of feeding behavior	GO:0060259	1.36E-03
response to extracellular stimulus	GO:0009991	1.5E-03
positive regulation of cold-induced thermogenesis	GO:0120162	1.56E-03
response to insulin	GO:0032868	3.71E-03
adaptive thermogenesis	GO:1990845	9.08E-03
negative regulation of peptide hormone secretion	GO:0090278	1.36E-02
regulation of bone remodeling	GO:0046850	1.5E-02
regulation of response to food	GO:0032095	1.64E-02
regulation of cold-induced thermogenesis	GO:0120161	1.87E-02
response to cold	GO:0009409	2.2E-02
cellular response to endogenous stimulus	GO:0071495	2.24E-02
regulation of angiogenesis	GO:0045765	2.25E-02
regulation of appetite	GO:0032098	2.33E-02
adult behavior	GO:0030534	2.64E-02
behavior	GO:0007610	2.83E-02
multicellular organismal process	GO:0032501	2.84E-02
regulation of response to nutrient levels	GO:0032107	4.33E-02
regulation of response to extracellular stimulus	GO:0032104	4.33E-02
peptide hormone secretion	GO:0030072	4.68E-02
negative regulation of angiogenesis	GO:0016525	4.68E-02
regulation of vasculature development	GO:1901342	4.92E-02

Table 1:


behavior
multicellular organismal process
negative regulation of peptide hormone secretion
feeding behavior
response to hormone
adaptive thermogenesis
semantic space Y
semantic space X
5
4
3
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-4
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-1
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3
4
5
6

Figure 1:

Discussion:

While the resulting GO enrichment wasn't significant, looking at the most significant of the overall insignificant results we can see certain trends and pathways that likely relate to obesity. From the chart above, we have "gastric inhibitory peptide signaling pathway", "cellular response to cortisol stimulus", "negative regulation of growth hormone receptor signaling pathway", "receptor catabolic process", "glucosamine catabolic process", "mitochondrial translational initiation", and "regulation of white fat cell proliferation."

We can further delve into details about how this list of pathways and mechanisms can affect obesity. Gastric inhibition likely affects digestive patterns and caloric uptake from ingested foods. Cortisol is a stress hormone that, when it is present in high concentration, can inhibit muscle synthesis and cause retention of fat. Growth hormones, conversely to cortisol, break down fats, so the negative regulation of growth hormone receptors can cause obesity. A couple of the next processes are catabolic processes, namely receptor catabolic process and glucosamine catabolic process. Catabolism, or the breaking down of molecules, is very crucial for determining metabolism and therefore obesity, so dysregulation in catabolic processes likely will cause obesity. Mitochondria are the energy generators of the body and therefore issues with mitochondrial translation can likely affect obesity. Finally, issues with regulation of white fat cell proliferation can cause an abundance of fat cells, and since fat cells typically only increase in quantity throughout human life, it can make someone have a much higher propensity to being obese.

Conclusion:

In conclusion, while the results were not necessarily significant according to the Gene Ontology tool, by sorting by the most significant of these results we found some pathways that likely do relate to obesity. Issues with gastric, hormonal such as growth hormone and cortisol, catabolic processes, and regulation of white fat cell proliferation all affect metabolic rates, fat cell number, and caloric uptake.