Is obesity a genetic disease? Human obese transcriptome analysis in monozygotic twins

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ABSTRACT

Obesity is a pandemic disease with a critical increase in childhood. An important unanswered question is to understand if this disease is due to genetic causes or to the life-style of the subjects. To address this question, we have analyzed if monozygotic twins show the same robust transcriptomic signature (5σ, as for the Higgs Boson) that we have recently revealed in obese subjects. Our results show that our signature correlates with BMI in paired transcriptomes of monozygotic twins, suggesting that the signature does not reflect underlying genetic causes.

Introduction

Obesity is a pandemic disease with an impressive increase in children.[1] The contribution to obesity of a genetic background is still debated. Well established cases of Mendelian forms of obesity approximately account for only 5% of the severely obese cases.[2] In the case of common obesity, recent genome wide association studies (GWAS) have investigated possible relations between single nucleotide polymorphism (SNP) and Body Mass Index (BMI).[3] Despite the sheer amount of data and the effort devoted to this task, none of the resulting genetic loci have real predictive power. In particular, genetic contributions do not account for most BMI variations between subjects which are likely due to lifestyle and environmental factors.[3] A recent paper reported the gene expression profile in subcutaneous adipose tissue of BMI-discordant monozygotic twin pairs without finding any molecular or clinical changes associated with subtypes of obesity.[4]

Recently, we revealed a robust transcriptomic signature of obesity by analyzing a collection of available datasets from adipocytes of obese subjects.[5] We were able to obtain a strong statistical significance (5σ as for the discovery of the Higgs boson) by eliminating batch effects due to the mixing of different datasets. The signature comprises 38 genes involved in the interaction between cells and the extracellular matrix, inflammation and central nervous system.[5]

In this brief note, we investigate if a Mendelian contribution to obesity is relevant for our signature. To this end, we check if our signature is correlated with BMI in paired transcriptomes of monozygotic twins.

Results

The transcriptomic signature of obesity

Here we give a brief overview of the derivation of the transcriptomic signature of obesity, inviting the interested reader to see[5] for details. Our analysis revolved around *SVDmerge* (https://github.com/ComplexityBiosystems/SVDmerge), an algorithm to remove batch effects, and *Pathway Deregulation Scores*, a pathway-based dimensionality reduction technique.[6] Combining these two methodologies allowed us to (i) merge several publicly available datasets, increasing the number of samples in the analysis, and (ii) transition from a gene-based to a pathway-based perspective, decreasing the number of variables from $\sim 20\,000$ genes to ~ 1000 pathways. In this way we substantially improved the samples-to-variables ratio and were able to identify pathways related to adhesion molecules, inflammation, salivary secretion and digestive problems. We also proposed a simple obesity score, computed as a linear combination of the expression of the 38 genes, and showed that it correlates well with BMI in several independent validation datasets. We verified that such correlations are gender-independent and tissue-specific. Finally, we pointed out that some of the deregulation patterns found in obesity are also seen in breast tumor samples.

It is interesting to compare our transcriptomic signature with existing results on obesity based on GWAS.[3] These studied have revealed a set of genetic loci that are associated with BMI variations. We have compared the list of genes in our signature with the list of genes reported in Ref.[3] as significantly associated with BMI. The two lists have no intersection. Similarly, the list of significant pathways revealed in Ref.[3] has no intersection with the list reported in.[5] Therefore, our approach allows to identify genes that normally are not highlighted because we are able to analyze more datasets due to the removal of batch effects by the method of single value decomposition.[5] The power of a Big Data analysis is actually to uncover things that are not easy to see, in this case genes and pathways at the roots of the problem.

Analysis of transcriptomes from BMI-discordant monozygotic twins

We applied the same strategy described in the previous section to study transcriptomic data from monozygotic (MZ) twins with discordant BMI, see Methods for details. Figure 1 shows that the obesity score correlates with BMI ($R = 0.68, p = 1.40 \times 10^{-4}$) considering all the 26 samples of the batch. This data set is particularly interesting because it consists of 26 samples from 13 MZ twin pairs whose BMI is highly discordant. Because MZ twins are genetically identical, BMI variations between a subject and its co-twin should be due exclusively to environmental factors and lifestyle. Figure 1b shows indeed that the variations in BMI correlate with variations in score ($R = 0.58, p = 3.80 \times 10^{-2}$) when considering only pairing between co-twins. We then perform a randomization test and compare changes in BMI and score in sets of 13 randomly chosen pairs of unrelated subjects. As shown in Figure 1c, there is no significant difference ($p = 0.35$) between the correlation in co-twins and the one in unrelated twins. Hence, the signature in co-twins reflects merely the BMI, rather than the genetic background that should be identical in co-twins and different in randomly paired subjects. This suggests that our transcriptomic signature is associated with obesity rather than with any underlying genetic differences in the subjects.

Conclusions

Rare genetic mutations in the leptin gene and elsewhere in the genome can cause extreme obesity, but the contribution of genetic over epigenetic and environmental factors in the current obesity pandemia is still debated. In this brief report, we show that obesity is correlated with a 38 genes transcriptomic signature in a BMI-dependent manner, even in subjects with the same genetic background. This suggests that pathway deregulation in obesity is linked to life-style rather than genes. Thus the only way to fight this disease is to work on the first aspect: If obesity is not due to the *bad luck* associated with inherited unlucky genes, each subject should in principle be able to reverse his/her condition by changing lifestyle.

Methods

Transcriptomic data

We use transcriptomes of 26 adipose tissue samples from 13 pairs of monozygotic twins with discordant BMI (BMI differences 3.3 – 10 $\mathrm{kg/m^2}$) from,[7] which can be accessed under identifier E-MEXP-1425 at the ArrayExpress repository. In particular, we use the files labeled as "processed" and, after averaging out probes that map to the same gene, apply a simple normalization imposing that the mean gene expression is constant among samples.

Obesity score

The obesity score S_j for sample j is calculated as a linear combination of the log2 expression of 38 genes:

$$S_j \equiv \sum_{r=1}^{n} \alpha_r X_{jr} \tag{1}$$

where α_r is the coefficient of the rank r gene in Table 1 and X_{jr} is its log2 expression in sample j. The set of 38 genes and their coefficients shown in Table 1 were determined in[5] using a dataset unrelated to the one analyzed in this manuscript. Obesity scores are displayed as mean-centered values in all figures.

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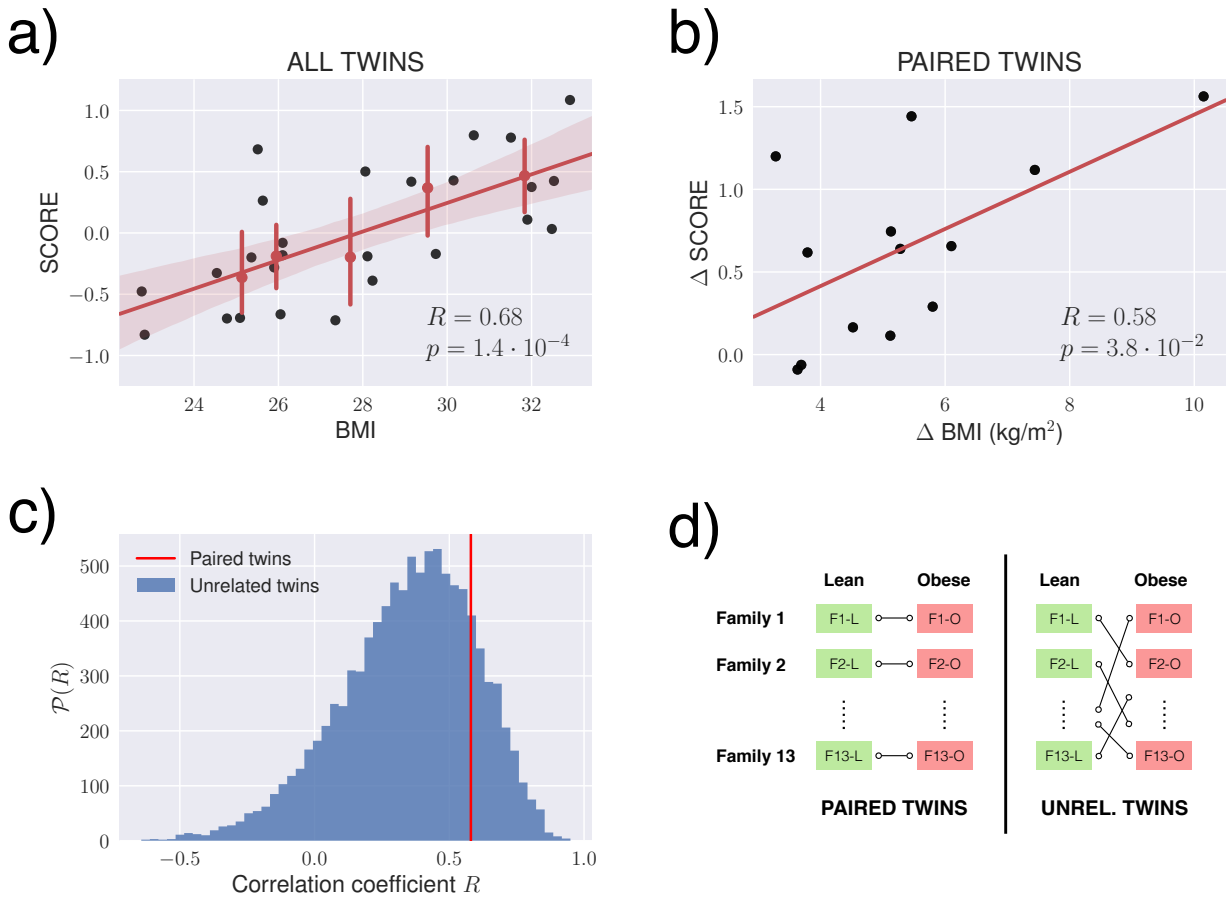

Figure 1. The obesity score in monozygotic twins. (a) Scatter plot of the obesity score versus BMI, for 26 adipose tissue samples corresponding to 13 pairs of monozygotic twins. (b) Scatter plot of change of obesity score versus change in BMI. Each point corresponds to a pair of twins, and change values are computed always as "obese co-twin versus lean co-twin". (c) Comparison of the correlation coefficient R associated to paired twins with those obtained from random samples of unrelated twins, see (d).

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FFC analyzed data. SZ and CAMLP designed the research and wrote the paper with the assistance of FFC.

rank	Entrez ID	Gene Symbol	Coefficient	rank	Entrez ID	Gene Symbol	Coefficient
1	1278	COL1A2	0.131	20	7045	TGFBI	0.0569
2	80763	SPX	−0.126	21	25878	MXRA5	0.0558
3	761	CA3	−0.0889	22	2982	GUCY1A3	0.0556
4	219348	PLAC9	0.0742	23	2335	FN1	0.0555
5	25975	EGFL6	0.0731	24	7076	TIMP1	0.0553
6	2014	EMP3	0.0701	25	5396	PRRX1	0.0548
7	6696	SPP1	0.0690	26	4069	LYZ	0.0529
8	1397	CRIP2	0.0679	27	8076	MFAP5	0.0510
9	1490	CTGF	0.0674	28	3512	JCHAIN	0.0486
10	22822	PHLDA1	0.0667	29	10402	ST3GAL6	−0.0466
11	1880	GPR183	0.0659	30	3429	IFI27	0.0458
12	171024	SYNPO2	0.0655	31	83442	SH3BGRL3	0.0457
13	1520	CTSS	0.0646	32	712	C1QA	0.0442
14	80114	BICC1	0.0638	33	474344	GIMAP6	0.0441
15	115207	KCTD12	0.0622	34	9457	FHL5	0.0438
16	151887	CCDC80	0.0599	35	8470	SORBS2	0.0437
17	22918	CD93	0.0591	36	7037	TFRC	0.0431
18	389136	VGLL3	0.0588	37	1291	COL6A1	0.0430
19	8542	APOL1	0.0581	38	57863	CADM3	0.0429

Table 1. The 38 genes in the transcriptomic signature of obesity and their associated coefficients. Genes are ranked by the absolute value of their coefficient. Details of how these genes and coefficients were computed can be found in.[5]

Additional information

Competing financial interests The authors declare no competing financial interests.