Genetically proxied growth differentiation factor 15 levels and body mass index

Ville Karhunen[1], Susanna Larsson[2], and Dipender Gill[3]

[1]Imperial College London
[2]Karolinska Institute
[3]St George's University Hospitals NHS Foundation Trust

January 17, 2021

Abstract

Growth-differentiation factor 15 (GDF15) is an inflammatory cytokine involved in energy homeostasis. Its circulating levels are acutely increased by the type 2 diabetes medication metformin, resulting in reduced appetite and weight loss. We identified a genetic variant at the GDF15 gene to proxy a small, lifelong increase in circulating GDF15 levels, and leveraged it in colocalization and Mendelian randomization analyses to investigate the effects of chronically elevated GDF15 levels on body mass index (BMI) and type 2 diabetes liability. The results provide human genetic evidence supporting that chronically elevated GDF15 levels increase BMI. There was no genetic evidence to support bi-directional effects, or that chronically elevated GDF15 levels directly affect liability to type 2 diabetes. Our results contrast the BMI lowering effects of an acute increase in GDF15 levels observed after metformin use. These findings have direct implications for informing pharmacological strategies aimed at targeting GDF15 levels for weight loss.

Introduction

Growth-differentiation factor 15 (GDF15) is an inflammatory cytokine involved in energy homeostasis[1]. Its circulating levels are acutely increased by the type 2 diabetes medication metformin, resulting in reduced appetite and weight loss[2]. However, the effect of chronically elevated circulating GDF15 levels on body weight is not known.

Here, we identified a genetic variant at the *GDF15* gene to proxy a small, lifelong increase in circulating GDF15 levels, and leveraged it in genetic analyses to investigate the effects of chronically elevated GDF15 levels on body mass index (BMI) and type 2 diabetes liability.

Methods

Colocalization and Mendelian randomization analyses were performed. Briefly, colocalization compares the proportionality of the genetic associations for two traits within a given genetic locus, investigating whether the data supports a model with a shared causal variant for both traits[3]. In Mendelian randomization, genetic variants that proxy the effect of varying the exposure are used to investigate its effect on an outcome[4]. Further details are provided in the Supplementary Methods.

Summary statistics data for the genetic associations of single-nucleotide polymorphisms with each trait were obtained from publicly available large-scale genome-wide association studies (GWAS) performed on individuals of European ancestries. These data can be obtained from the original studies, as detailed below. Genetic associations with circulating GDF15 levels were based on 3,301 healthy individuals[5], genetic associations with BMI were obtained from a GWAS meta-analysis of 806,834 individuals[6], and genetic associations

with type 2 diabetes liability were based on a GWAS meta-analysis of 74,124 cases and 824,006 controls[7]. Relevant ethical approval and participant consent were obtained by the original studies.

Results

Colocalization analysis within the *GDF15* gene supported the model with a shared causal genetic variant (posterior probability > 0.99; Figure) for GDF15 levels and BMI, with rs16982345 identified as the most likely shared causal variant. In Mendelian randomization analysis using the rs16982345 variant, genetically proxied higher circulating GDF15 levels were associated with increased BMI (change in standard deviation [SD] units per one SD increase in GDF15 levels: 0.021 [95% confidence interval 0.014 to 0.028], $p = 4 \times 10^{-9}$). Exploring bi-directional effects, there was no evidence of genetically proxied BMI being associated with GDF15 levels (change in SD units per one SD increase in BMI: 0.005 [95% confidence interval -0.133 to 0.143], p = 0.95). There was no strong evidence for colocalization of GDF15 levels and type 2 diabetes liability (posterior probability = 0.16).

Discussion

Using human data, we provide genetic evidence supporting the notion that chronically elevated GDF15 levels increase BMI. There was no genetic evidence to support bi-directional effects, or that chronically elevated GDF15 levels directly affect liability to type 2 diabetes. Our results contrast the BMI lowering effects of an acute increase in GDF15 levels observed after metformin use[2]. One possible explanation for this discrepancy is that chronic elevation of circulating GDF15 levels leads to desensitization of the GDF15 receptor and reduced signaling[8].

The use of both colocalization and Mendelian randomization in this study provide complementary evidence supporting causal effects of chronically elevated GDF15 levels on BMI. As genetic variants are randomly allocated at conception, the Mendelian randomization paradigm is less susceptible to the confounding and reverse causation that that can hinder causal inference in observational studies. As a limitation of this work, the genetic associations were derived from individuals of European ancestries, and therefore our results may not generalize to other ethnic groups.

In conclusion, this genetic analysis found robust evidence to support that, in contrast to acute elevations in GDF15 levels, chronically elevated GDF15 levels increase BMI. These findings may be used to inform the design of pharmacological strategies aimed at targeting GDF15 for weight loss.

References

1. Tsai VWW, Husaini Y, Sainsbury A, Brown DA, Breit SN. The MIC-1/GDF15-GFRAL Pathway in Energy Homeostasis: Implications for Obesity, Cachexia, and Other Associated Diseases. *Cell Metabolism* . 2018/09/04/ 2018;28(3):353-368. doi:https://doi.org/10.1016/j.cmet.2018.07.018

2. Coll AP, Chen M, Taskar P, et al. GDF15 mediates the effects of metformin on body weight and energy balance. *Nature* . 2020/02/01 2020;578(7795):444-448. doi:10.1038/s41586-019-1911-y

3. Giambartolomei C, Vukcevic D, Schadt EE, et al. Bayesian Test for Colocalisation between Pairs of Genetic Association Studies Using Summary Statistics. *PLOS Genetics* . 2014;10(5):e1004383. doi:10.1371/journal.pgen.1004383

4. Davey Smith G, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease?*. *International Journal of Epidemiology* . 2003;32(1):1-22. doi:10.1093/ije/dyg070

5. Sun BB, Maranville JC, Peters JE, et al. Genomic atlas of the human plasma proteome. *Nature* . 2018/06/01 2018;558(7708):73-79. doi:10.1038/s41586-018-0175-2

6. Pulit SL, Stoneman C, Morris AP, et al. Meta-analysis of genome-wide association studies for body fat distribution in 694 649 individuals of European ancestry. *Human Molecular Genetics* . 2018;28(1):166-174. doi:10.1093/hmg/ddy327

7. Mahajan A, Taliun D, Thurner M, et al. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. *Nature Genetics* . 2018/11/01 2018;50(11):1505-1513. doi:10.1038/s41588-018-0241-6

8. Eddy AC, Trask AJ. Growth Differentiation Factor-15 and Its Role in Diabetes and Cardiovascular Disease. *Cytokine & Growth Factor Reviews* . 2020/12/01/ 2020;doi:https://doi.org/10.1016/j.cytogfr.2020.11.002

Figure. Colocalization plot of genetic associations for circulating growth differentiation factor 15 levels and body mass index within ±10 kb of *GDF15* gene. LD = linkage disequilibriumr^2 with rs16982345, the variant identified as the most likely shared causal variant.