

**SHORT REPORT**

# Genetically proxied growth-differentiation factor 15 levels and body mass index

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Growth-differentiation factor 15 (GDF15) is an inflammatory cytokine involved in energy homeostasis that is being pursued as a drug target for obesity. 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.

**KEYWORDS**

body mass index, colocalization, growth-differentiation factor 15, Mendelian randomization, type 2 diabetes

**Principal investigator statement:** This study did not perform any intervention on human subjects and, as such, no Principal Investigator Statement is required.

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## 1 | INTRODUCTION

Growth-differentiation factor 15 (GDF15) is an inflammatory cytokine involved in energy homeostasis that is being pursued as a drug target for obesity.<sup>1</sup> Its circulating levels are acutely increased by the type 2 diabetes medication metformin, resulting in reduced appetite and weight loss.<sup>2</sup> 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.

## 2 | METHODS

Colocalization and Mendelian randomization analyses were performed. Briefly, colocalization compares the genetic associations for two traits within a given genetic locus, investigating whether the data support a model with a shared causal variant for both traits.<sup>3</sup> In Mendelian randomization, genetic variants that proxy the effect of varying the exposure are used to investigate their effect on an outcome.<sup>4</sup> Our choice of genetic proxy for the effect of GDF15 signalling was restricted to a variant at the *GDF15* locus, to reduce the risk of bias related to pleiotropic associations unrelated to GDF15.<sup>5</sup> Further details are provided in the Supporting Information.

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 3301 healthy individuals,<sup>6</sup> genetic associations with BMI were obtained from a GWAS meta-analysis of 806 834 individuals,<sup>7</sup> and genetic associations with type 2 diabetes liability were based on a GWAS meta-analysis of 74 124 cases and 824 006 controls.<sup>8</sup> Relevant ethical approval and participant consent were obtained by the original studies.

## 3 | RESULTS

Colocalization analysis within the *GDF15* gene supported the model with a shared causal genetic variant (posterior probability > 0.99; Figure 1) for GDF15 levels and BMI, with rs16982345 identified as the most likely shared causal variant ( $P = 5.8 \times 10^{-99}$  for the association with GDF15 levels, and  $P = 4.4 \times 10^{-9}$  for the association with BMI). 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 0.014–0.028],  $P = 4.4 \times 10^{-9}$ ). Exploring bi-directional effects, there was no evidence of genetically proxied BMI being

### What is already known about this subject

- Growth-differentiation factor 15 is an inflammatory cytokine involved in energy homeostasis that is being pursued as a drug target for obesity.
- Circulating levels of growth-differentiation factor 15 are acutely increased by the type 2 diabetes medication metformin, resulting in reduced appetite and weight loss.
- However, the effect of chronically elevated circulating growth-differentiation factor 15 levels on body weight is not known.

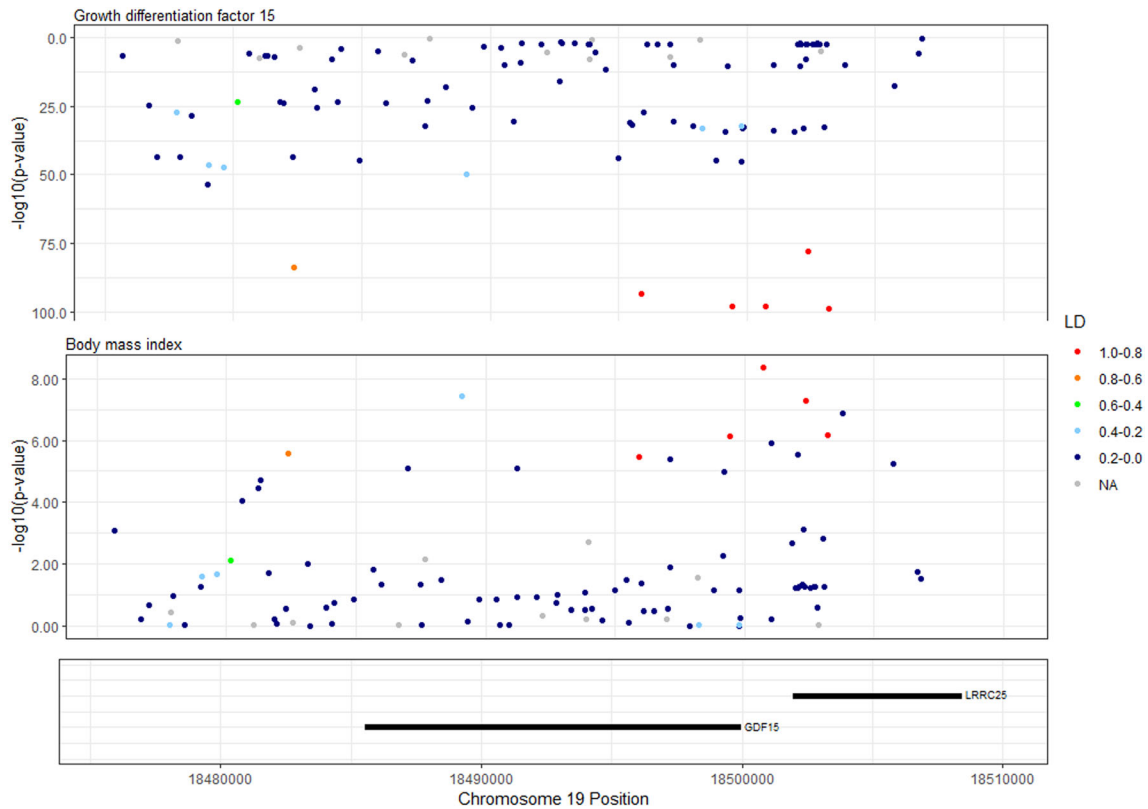
### What this study adds

- Using human data, this study provides genetic evidence supporting that chronically elevated circulating growth-differentiation factor 15 levels increase body mass index.
- There was no genetic evidence to support bi-directional effects, or that chronically elevated growth-differentiation factor 15 levels directly affect liability to type 2 diabetes.
- These results contrast the BMI-lowering effects of an acute increase in growth-differentiation factor 15 levels observed after metformin use.
- These findings have direct implications for informing pharmacological strategies aimed at targeting growth-differentiation factor 15 levels for weight loss.

associated with GDF15 levels (change in SD units per one SD increase in BMI [95% confidence interval]: inverse-variance weighted estimate 0.005 [–0.133 to 0.143],  $P = .95$ ; weighted median estimate: –0.059 [–0.260 to 0.143],  $P = .57$ ; MR-Egger estimate –0.104 [–0.485 to 0.277],  $P = .59$ ; MR-Egger intercept test for directional pleiotropy:  $P = .55$ ). There was no strong evidence for colocalization of GDF15 levels and type 2 diabetes liability (posterior probability = 0.16).

## 4 | 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 with the BMI-lowering effects of an acute increase in GDF15 levels observed after metformin use.<sup>2</sup> There are a number of possible explanations for this discrepancy, including that metformin may be affecting BMI through mechanisms unrelated to GDF15. Long-term elevation of circulating GDF15 levels may also contrast the effects of acute increases in GDF15 and lead to desensitization of the



**FIGURE 1** Colocalization plot of genetic associations for circulating growth differentiation factor 15 levels and body mass index within  $\pm 10$  kb of *GDF15* gene. LD, linkage disequilibrium  $r^2$  with rs16982345, the variant identified as the most likely shared causal variant

*GDF15* receptor and reduced signalling.<sup>9</sup> Alternative possibilities include compensatory changes in other hormones and behaviours (including dietary intake) as a result of elevated circulating *GDF15* levels. Furthermore, it is possible that *GDF15* affects fetal and childhood development, thus impacting adult BMI through this mechanism.

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 can hinder causal inference in observational studies. A previous Mendelian randomization analysis exploring the effect of circulating *GDF15* levels on BMI used variants from throughout the genome in their main analysis.<sup>10</sup> While the greater number of variants generated through this strategy allows for the incorporation of Mendelian randomization statistical sensitivity analyses, this approach also risks including variants that have pleiotropic associations unrelated to *GDF15*, which can consequently bias the Mendelian randomization analysis.<sup>5</sup> Previous Mendelian randomization studies exploring the effect of circulating *GDF15* have also used *GDF15* genetic association estimates that were adjusted for systolic blood pressure, antihypertensive medication use, diabetes mellitus and smoking status,<sup>10,11</sup> which can introduce collider bias.<sup>12</sup> Another previous study used a genetic variant related to *GDF15* gene expression in whole blood to

proxy the effect of varying *GDF15* circulating levels.<sup>13</sup> However, colocalization analysis was not performed in this work, so it is unclear whether genetic confounding was introducing bias into consequent Mendelian randomization analysis.<sup>13</sup> Such issues potentially explain the discrepancy in the results of these previous studies with our current work, which did not suffer from the same limitations.

As a limitation of our current work, the genetic associations were derived from individuals of European ancestries, and therefore our results may not generalize to other ethnic groups. A further limitation is that we used BMI as a measure of obesity. However, BMI may also be elevated in the context of increased lean mass and body water content, and is not always reflective of increased body fat.

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.

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## COMPETING INTERESTS

D.G. is employed part-time by Novo Nordisk. The remaining authors declare that there are no relationships or activities that might bias, or perceived to bias, this work.

## CONTRIBUTORS

All authors substantially contributed to the conception and design of the work. V.K. conducted the statistical analyses and drafted the manuscript. All authors interpreted the data, critically revised the manuscript and provided final approval of the version to be submitted. V.K. and D.G. are the guarantors of the work.

## DATA AVAILABILITY STATEMENT

All data used in this study are publicly available, with the relevant citations detailed.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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