Genetic evidence supporting fibroblast growth factor 21 signalling as a pharmacological target for cardiometabolic outcomes and Alzheimer's disease

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Abstract

Fibroblast growth factor 21 (FGF21) is a human metabolic hormone that is being pursued in early stage clinical trials as pharmacological target to treat a range of metabolic diseases. In animal models, increased FGF21 signalling has been shown to have beneficial effects on cardiometabolic outcomes, Alzheimer's disease risk and lifespan. However, studies investigating the effect of FGF21 signalling on these clinical outcomes in humans have been inconclusive. In this study, a genetic variant associated with higher circulating FGF21 levels was leveraged to investigate its clinical effects in humans. Higher genetically proxied circulating FGF21 levels were associated favourably with lipid levels, blood pressure traits, waist-to-hip ratio, chronic inflammation, cardiovascular outcomes, Alzheimer's disease risk and lifespan. These findings may be used to anticipate the effects of pharmacologically increasing FGF21 signalling and inform the design of further clinical trials.

Introduction

Fibroblast growth factor 21 (FGF21) is a human metabolic hormone that is expressed in the liver, pancreas, skeletal muscle, adipocytes and brain.[1] The effects of FGF21 signalling include altering of lipid metabolism and macronutrient preference.[1, 2] Increased circulating FGF21 levels decrease the consumption of sweets and alcohol, but increase dietary protein intake.[2] In rodents and non-human primates, increased FGF21 signalling has beneficial effects on cardiometabolic outcomes, such as reduction in fat mass and alleviation of hyperglycaemia, insulin resistance, dyslipidaemia, and cardiovascular diseases.[3] Furthermore, FGF21 has also been implicated in protecting against Alzheimer's disease,[4] as well as improving lifespan.[5] However, studies investigating the effect of FGF21 signalling on these clinical outcomes in humans have been inconclusive.[3, 6] To prioritise the design of future clinical trials pharmacologically targeting FGF21,[7] we aimed to leverage human genetic data within the Mendelian randomization paradigm to investigate the effects of higher genetically proxied circulating FGF21 levels on cardiometabolic outcomes, Alzheimer's disease and lifespan.[8]

Methods

All data used for this work are publicly available, as detailed below. Circulating FGF21 concentration was proxied by a genetic variant (rs838133) in the *FGF21* gene region, previously shown to be associated with fasting plasma FGF21[9] as well as with intake of macronutrients, alcohol and sweets.[6, 9]Publicly available summary-level data for the associations of the FGF21 variant with macronutrient and alcohol intake and other outcomes were obtained from UK Biobank and genome-wide association study consortia. Details of the outcome datasets used in this study are provided in Table 1.

Results

We first investigated the association between the FGF21 variant and macronutrient and alcohol intake. The G (major) allele of rs838133 was associated with lower intake of total sugars and alcohol, and higher intakes of protein and fat (Figure 1), consistent with the expected effect of an increase in FGF21 concentration.[2] We scaled all results per additional G allele to mimic the effect of elevated FGF21 concentrations.

Higher genetically proxied FGF21 concentration was associated with greater body mass index, body fat percentage and waist and hip circumferences, but with lower waist-to-hip ratio (Figure 1). Additionally, higher genetically proxied FGF21 concentration was associated with lower concentrations of low-density lipoprotein cholesterol and triglycerides, lower systolic and diastolic blood pressure, and lower C-reactive protein concentrations, but was not associated with fasting glucose or fasting insulin (Figure 1). There was a positive association of higher genetically proxied FGF21 concentration with the liver enzyme alkaline phosphatase, but a negative association with aspartate aminotransferase, gamma glutamyltransferase, and direct and total bilirubin concentrations (Figure 1). There was suggestive evidence of a positive association between genetically proxied FGF21 concentration and lifespan (based on parental lifespan) (Figure 1).

In analyses of cardiovascular diseases, higher genetically predicted FGF21 concentration was strongly associated with a reduced risk of venous thromboembolism, and had suggestive inverse associations with coronary artery disease, heart failure, and ischemic stroke (Figure 2). There was a suggestive association of higher genetically proxied FGF21 concentration with reduced risk of Alzheimer's disease (based on clinically diagnosed Alzheimer's disease and Alzheimer's disease by proxy cases and their corresponding controls), but no association with type 2 diabetes (Figure 2).

Discussion

FGF21 signalling is being pursued as a pharmacological target in early stage clinical trials.[7] Our current study leveraged genetic data to provide insight into the broad metabolic and clinical effects of FGF21 in humans. The results support previously reported associations of genetically proxied circulating FGF21 levels with lipid levels, blood pressure, fat mass, and liver enzymes as well as the lack of association with type 2 diabetes.[6] Our present study went further to provide novel evidence that increased FGF21 signalling decreases chronic inflammation measured using C-reactive protein). We also identified a potential beneficial effect of FGF21 on cardiovascular outcomes. Additionally, our results support a beneficial effect of higher circulating FGF21 levels on Alzheimer's disease and lifespan.

These findings inform on the potential effects of pharmacologically increasing FGF21 levels and signalling. Of note, the genetic variant used to proxy FGF21 levels reflects small, lifelong increases in FGF21 levels, and the results therefore inform on the effects of elevating circulating FGF21 levels and signalling in the long-term. The limitations of this study should also be acknowledged. Critically, it is possible that some of the identified associations may be attributable to genetic confounding, where the genetic variant used to proxy circulating FGF21 also has pleiotropic associations unrelated to FGF21. As summary genetic association data for circulating FGF21 levels were not available, we could not perform colocalization analysis to explore this.[10] Furthermore, the outcomes that we studied were determined by the availability of corresponding large-scale genetic association summary data. As such, it was not possible to perform analyses for other relevant traits, such as non-alcoholic steatohepatitis.

In summary, we used a human genetic proxy for higher circulating FGF21 levels to identify evidence for favourable effects of its signalling in humans on a range of cardiometabolic outcomes, Alzheimer's disease and lifespan. This work should be used to inform the design of further clinical studies.

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Figure 1. Associations of higher genetically predicted Fibroblast Growth Factor 21 (FGF21) concentration with macronutrient intake, anthropometric and cardiometabolic traits, and liver enzymes. Estimates are scaled per additional FGF21-increasing allele of rs838133. The outcomes are in standard deviation units except for fasting glucose (in nmmol/L), fasting insulin (in pmol/L) and lifespan (in years). CI: confidence interval.

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Figure 2. Associations of higher genetically predicted Fibroblast Growth Factor 21 (FGF21) concentration with cardiometabolic diseases, Alzheimer's disease and lifespan. Estimates are scaled per additional FGF21-increasing allele of rs838133. CI: confidence interval; OR: odds ratio.

Table 1. Data sources for the outcome phenotypes included in the present Mendelian randomization study

Outcome phenotype*	**ID for the outcomes obtained through the MR Base platform or name of the out**
Macronutrient/alcohol	
Total sugar intake+	ukb-b-17079; 100008: Output from GWAS pipeline using Phesant derived variables from UK
Carbohydrate intake+	ukb-b-7244; 100005: Output from GWAS pipeline using Phesant derived variables from UKB
Protein intake+	ukb-b-12043; 100003: Output from GWAS pipeline using Phesant derived variables from UK
Fat intake+	ukb-b-12379: 100004: Output from GWAS pipeline using Phesant derived variables from UK
Alcohol intake+	ukb-b-5359; 100022: Output from GWAS pipeline using Phesant derived variables from UKB
Anthropometric trait	
Body mass index	NA
Waist circumference	ukb-b-9405; 48: Output from GWAS pipeline using Phesant derived variables from UKBB (M
Hip circumference	ukb-b-15590; 49: Output from GWAS pipeline using Phesant derived variables from UKBiob
Waist-to-hip ratio	NA
Body fat percentage	ukb-b-8909; 23099: Output from GWAS pipeline using Phesant derived variables from UKBI
Cardiometabolic trait	
Fasting glucose	ebi-a-GCST005186
Fasting insulin	ebi-a-GCST005185
Triglycerides	ieu-a-302
LDL cholesterol	ieu-a-300
HDL cholesterol	ieu-a-299
Systolic blood pressure	ukb-b-20175; 4080: Output from GWAS pipeline using Phesant derived variables from UKBI

Outcome phenotype*	**ID for the outcomes obtained through the MR Base platform or name of the out**
Diastolic blood pressure	ukb-b-7992; 4079: Output from GWAS pipeline using Phesant derived variables from UKBB
C-reactive protein level	NA
Liver enzyme/metabolite	
Alanine aminotransferase	ukb-d-30620_irnt
Alkaline phosphatase	ukb-d-30610_irnt
Aspartate aminotransferase	ukb-d-30650_irnt
Gamma glutamyltransferase	ukb-d-30730_irnt
Direct bilirubin	ukb-d-30660_irnt
Total bilirubin	ukb-d-30840_irnt
Cardiometabolic disease	
Coronary artery disease	ebi-a-GCST005195
Coronary artery disease	I9_IHD
Heart failure	NA
Heart failure	I9_HEARTFAIL
Atrial fibrillation	ebi-a-GCST006414
Atrial fibrillation	I9_AF
Ischemic stroke	NA
Ischemic stroke	ukb-d-I9_STR_EXH
Ischemic stroke	I9_STR_EXH
Venous thromboembolism	ukb-d-I9_VTE
Venous thromboembolism	I9_VTE
Type 2 diabetes	NA
Type 2 diabetes	E4_DM2_STRICT (exclude type 1 diabetes)
Other outcomes	
Alzheimer's disease	NA
Parental lifespan	NA

GLGC, Global Lipids Genetics Consortium; HDL, high-density lipoprotein; HERMES, Heart Failure Molecular Epidemiology for Therapeutic Targets; ICBP, International Consortium of Blood Pressure; LDL, low-density lipoprotein; MAGIC, Meta-Analyses of Glucose and Insulin-related traits Consortium; NA, not available; UK Biobank, UKBB.

*The genetic association summary statistics estimates were extracted from the MR-Base platform[11], publicly available genetic consortia data, or the last public release (R4) of the FinnGen consortium.[16]

+Estimated nutrient intake based on UKBB participants' answers to the dietary questionnaire.

++Three independent consortia, including Alzheimer's disease working group of the Psychiatric Genomics Consortium (PGC-ALZ), the International Genomics of Alzheimer's Project (IGAP), and the Alzheimer's Disease Sequencing Project (ADSP).

§The dataset consists of 24 087 clinically diagnosed late-onset Alzheimer's disease cases, paired with 55 058 controls plus the AD-by-proxy phenotype, based on individuals in the UK Biobank (UKB) for whom parental Alzheimer's disease status was available (proxy cases = 47 793; proxy controls = 328 320).