Loss of function variant in *SMIM1* is associated with reduced energy expenditure and weight gain

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Abstract

Blood group antigens are the archetypal example of human genetic variation. Here, we characterised the functional metabolic consequences in individuals homozygous for a 17bp deletion in *SMIM1* (rs566629828; minor allele frequency 0.0147) and thus lacking the protein defining the Vel blood group. Our analysis, in separate cohorts of *SMIM1*^{-/-} individuals (UK Biobank, NHS Blood and Transplant, Danish Blood Donor Study, Copenhagen Hospital Biobank) and a mouse model, identified an increase in body weight accompanied by a range of metabolic differences, including dyslipidemia, changes in the leptin-adiponectin ratio, increased liver enzymes and lower total thyroid hormone levels. These changes in the metabolic state were at least in part due to a reduction in resting energy expenditure, as assessed during an in-depth clinical assessment of *SMIM1*^{-/-} individuals. Additionally, electronic health records suggest that individuals lacking this 78-amino-acid type II transmembrane protein may be more prone to cerebral bleeds and thrombotic stroke.

Main text

Over 1500 variants in 48 genes underlie the range of antigens categorised into 43 blood group systems. Common loss-of-function (LoF) variants in the *ABO* and *RHD*

(Rhesus) genes result in the absence of the A, B and D antigens from red cells and other tissues^{1,2}. These LoF variants are important in matching blood for transfusion and for instance, fetuses of D-negative pregnant women are at risk of haemolytic disease. Genome-wide association studies have shown that common variants at *ABO* and *RHD* are associated with the risk of several diseases, as well as, being associated with blood cell traits^{3,4}. In contrast, rare LoF variants in a few blood group genes, when present in homozygosity or compound heterozygosity, are causal of extremely rare inherited diseases¹.

Changes in lifestyle, coupled with a genetic component, have led to a steep increase in obesity and associated pathologies rates⁵. Here, we characterised individuals homozygous for the 17bp deletion in *SMIM1* (rs566629828), who lack the SMIM1 protein from all tissues (hereafter *SMIM1*^{-/-}), and their red cells have no detectable Vel antigen (**Fig.S1**)^{6–8}. We identified 104 participants with this genotype in 488,376 UK Biobank (UKB) participants, 90 being unrelated and of European ancestry⁹ (46 females and 44 males; **Methods** and **Fig.S2, Table S1**), corroborating the previously reported minor allele frequency (MAF) for this deletion in this population⁶ and thus estimating the number of *SMIM1*^{-/-} individuals at around 150,000 in Europe alone. The 17bp deletion is in high linkage disequilibrium (D' 0.98) with the minor (G) allele of rs1175550 (MAF 0.23), a strong sentinel eQTL for *SMIM1* in the blood^{10,11} (www.eqtlgen.org) and associated with red cell traits independently of rs566629828 (**Fig.S1**).

Interestingly, leveraging on the richness of data in the UKB cohort, we were able to associate *SMIM1*^{-/-} participants with increased weight (linear regression, **Fig.1A, Fig.S2** and **Table S1**). This analysis indicated an autosomal recessive effect, therefore we considered only *SMIM1*^{+/+} and *-/-* individuals for the subsequent analyses. These showed further association with body mass index (BMI), waist circumference and both arms' fat mass (**Fig.1B**). The effect sizes ($\hat{\beta}$) estimated from UKB measurements ranged between 0.22 and 0.27 standard deviations (sd) with all FDR values below 0.05 (**Table S1**). For weight, these differences equate to an average extra 4.6kg in females and 2.4kg in males (**Table S1**). Analysis of UKB plasma biochemistry assays showed that *SMIM1*^{-/-} participants had greater levels of triglycerides (TG; $\hat{\beta}$ =0.3 FDR=1.07e-2; **Fig.1B** and **1C**). Furthermore, they exhibited greater average levels of

liver enzymes with $\hat{\beta}$ for alanine and aspartate aminotransferase (ALT and AST) of 0.50, and 0.43 and for gamma-glutamyl transferase (GTT) of 0.35 (FDR: 4.10e-06, 5.01e-05 and 2.49e-03, respectively), as well as increased urate levels ($\hat{\beta}$ =0.35, FDR=3.54e-04; **Fig.1B** and **1C**, **Table S1**). Regression analysis, adjusting for the effects of BMI, removed the associations with body composition features. However, the associations with TG, liver enzymes and urate levels were only attenuated (**Fig.1C** and **Table S1**), suggesting that these effects were not solely dependent on BMI. Interestingly, we identified also sex-specific effects. *SMIM1*^{-/-} female UKB participants exhibit greater average fat-free mass in arms and legs (right arm $\hat{\beta}$ =0.39, FDR=2.39e-02; right leg $\hat{\beta}$ =0.33, FDR=6.01e-02; **Table S1**) and lower average sex hormone binding globulin levels (SHBG; $\hat{\beta}$ =-0.41, FDR=2.93e-2). Additional sex-specific differences were noted and are presented in **Table S1**. *Smim1* knock-out (*Smim1*^{-/-}) mice recapitulated the increased weight observed in UKB. *Smim1*^{-/-} females weight trajectories over time were, on a chow diet, steeper than those of their control littermates already in the first 30 weeks (**Fig.1D**; linear regression, $\hat{\beta}$ =0.53, P =2.52e-2; **Table S2**). The effects in males, albeit showing a similar trend, were not significant in the timeframe analysed (**Fig.1D**).

Importantly, (i) none of the above associations were detected in carriers (single copy) of the 17bp deletion; (ii) none of the above associations were detected for the common eQTL variant rs1175550, suggesting that the metabolic differences were unlikely to be mediated by rs1175550-associated variation in the expression of *SMIM1* in red cells¹¹; (iii) even when we observed differences between *SMIM1*^{+/+} and ^{-/-} individuals, the mean values for the two groups were within the normal ranges for each measurement, (iv) no association was found between *SMIM1*^{-/-} and fasting glucose levels in the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) results¹².

To further investigate these findings, we made home visits to obtain blood samples and health data from 25 British *SMIM1*^{-/-} individuals (12 females, 13 males; not UKB participants, **Fig.S2**) for an extensive survey of metabolism relevant analytes, with results being compared with 180 individuals (100 females, 80 males) who carried at least one reference allele for variant rs566629828; both groups were registered donors with NHS Blood and Transplant (NHSBT; all values in **Table S3**). We observed the same trend for *SMIM1*^{-/-} individuals to be heavier but, possibly, because of the small

sample size, the significance threshold was not reached (**Table S4**). We replicated the associations between *SMIM1*^{-/-} for increased average levels for ALT and AST with the same order of magnitude as observed in UKB (**Fig.2, Table S4**). We also found associations between *SMIM1*^{-/-} and increased leptin to adiponectin ratio (LAR; $\hat{\beta}=0.53$, FDR=2.58e-02), and an increase in free fatty acids (FFA; $\hat{\beta}=1.18$, FDR=1.42e-06), two indices of increased fat mass and insulin resistance (**Fig.2A and 2B**)^{13,14}. Moreover, we found that *SMIM1*^{-/-} individuals have lower average levels of total triiodothyronine and thyroxine (T3; $\hat{\beta}=-0.86$, FDR=9.87e-04; T4; $\hat{\beta}=-0.74$, FDR=2.84e-03; **Fig.2A and 2B**) and that levels of thyroid stimulating hormone (TSH) seemed to be lower (**Table S4**).

The above findings prompted us to invite 12 *SMIM1*^{-/-} individuals belonging to the NHSBT cohort for a 2-day metabolic assessment (**Fig.S2**). We estimated the effect of the absence of *SMIM1* on resting energy expenditure (REE; a marker of whole body metabolic activity) by indirect calorimetry and body mass composition by dual-energy X-ray absorptiometry (DXA), using a well-established protocol¹⁵ (**Methods**). These studies showed that *SMIM1*^{-/-} individuals had a lower REE adjusted for lean mass (**Fig.2C**, x-axis; Welch Two Sample t-test; $P=7.62e-04$, **Table S5**), whilst there were no differences in average lean mass compared to 310 unselected controls (**Table S5**). Average free T3, but not free T4, measurements were lower in the 12 *SMIM1*^{-/-} than in the controls group (**Table S3 and S4**) and changes in physique seen in the 90 *SMIM1*^{-/-} UKB participants were reflected in abnormal body composition visualised by DXA scans (**Fig.2D**). Because of the effect on REE and T3 and T4 levels, we explored the possible involvement of *SMIM1* in the hypothalamic-pituitary-thyroid axis¹⁶. We analysed the single-cell RNA-sequencing data in studies that dissected the transcript levels of these tissues in multiple organisms. In the mouse hypothalamus¹⁷ (GSE113576), *Smim1* was expressed at low levels in mature oligodendrocytes and some, but not all, inhibitory neurons (**Fig.S3A**). Its expression was largely non-overlapping with that of the thyrotropin-releasing hormone (TRH; **Fig.S3B**). In the human anterior pituitary gland¹⁸ (GSE142653), *SMIM1* was found expressed in corticotropes, gonadotropes and somatotropes (**Fig.S3C**). Whilst, in human thyroid organoids and mouse thyroid¹⁹ (GSE163818) low-level expression was detected mainly in thyrocytes and as yet uncharacterised Flt1-positive cells (**Fig.S3C**). These

analyses indicate that *SMIM1* could play one or more roles in the hypothalamic-pituitary-thyroid axis.

The associations between the genotype at rs566629828 and phenotypes observed in the UKB and NHSBT cohorts were orthogonally validated in 73 Danish *SMIM1*^{-/-} individuals from the Danish Blood Donor Study²⁰ (DBDS; 25 female, 18 male, and 645 controls), and the Copenhagen Hospital Biobank²¹ (CHB; 12 female, 18 male, and 450 matched controls). Weight data, available only for the DBDS participants, showed, upon bootstrapping analysis (**Methods**; controls matched by age, sex and smoking status), consistent directionality for female *SMIM1*^{-/-} individuals. However, the low number of Danish *SMIM1*^{-/-} individuals and a less evident effect on weight in males (**Fig.1B**) limited the statistical power to detect differences. Interestingly, 20 of the 73 (27%) *SMIM1*^{-/-} individuals in the Danish cohorts were assigned a diagnosis of disorders of lipoprotein metabolism versus only 13% in the controls (OR=4.07, FDR=2.09e-04). A review of all prescriptions in both cohorts showed greater use of statins in individuals lacking *SMIM1* versus controls (OR=2.36, FDR=2.22e-02; **Table S6**) indicating a high level of individuals considered ‘at risk’ of cardiovascular events.

Interestingly an exploratory analysis of hospital episode statistics revealed an increased risk for cerebral events, with 5 cerebral bleeds and 5 thrombotic strokes in the 65 *SMIM1*^{-/-} UKB participants for whom data were available (OR=5.53 and 3.46, FDR=6.88e-04 and 2.32e-02, respectively; **Table S7**).

In summary, we identified a loss-of-function variant which is present in homozygosity in 1 in 5,000 individuals in Great Britain and with even higher frequency in the Nordic countries (this manuscript and reference⁷). The MAF of rs566629828 is at the interface between common and rare variation, and has one of the largest effects on weight ($\hat{\beta}$ =0.22) and BMI ($\hat{\beta}$ =0.27) reported so far with the exception of extremely rare variants directly implicated in lipid metabolism²². Our findings show that *SMIM1*^{-/-} individuals (Vei negative blood group) exhibit a combination of metabolic features including increased fat mass, inflammation, triglycerides and altered lipoprotein metabolism due, at least in part, to reduced energy expenditure, a major risk factor in obesity^{23,24}. Some of these associations, like urate and GGT, were driven by the effect being stronger in one sex; others, like SHBG and LDL, were found only in one of the two sexes, females and males respectively. In the more extreme cases, these effects

could lead to insulin resistance and metabolic syndrome accompanied by increased susceptibility to cardiovascular disease, as is supported by analysis of electronic hospital records, which indicated that these individuals may be more prone to cerebral bleeds and thrombotic stroke. All together the observed metabolic phenotype and increased risk for cardiovascular events is compatible with the notion that the absence of the SMIM1 protein results in a state of mild hypothyroidism.

The quantity of genomic data available, including blood donors typed by arrays², is growing rapidly, as is the number of individuals identified as *SMIM1*^{-/-}. Future studies should investigate how adverse metabolic phenotype and pituitary-thyroid axis abnormalities are linked to the deficiency of this small, transmembrane protein of unknown function, and whether thyroid hormone supplementation can reverse cardiometabolic risk associated with this unique condition.

Methods

A total of 188 *SMIM1*^{-/-} individuals (101 females, 87 males) from four different cohorts (UKB, NHSBT, DBDS, CHB) were included in the study. For an overview of the cohorts, see **Fig.S2**.

UK Biobank

The UKB analyses have been conducted under application number 13745. The UKB cohort consists of 502,682 participants, aged between 40 and 69 years of age on enrollment, recruited at 22 assessment centres across the UK between 2006 and 2010²⁵. DNA samples were taken from participants and genotyped using the UK Biobank Axiom Array on the GeneTitan (Affymetrix, Santa Clara, CA). Genotype calling and quality control of the UKB dataset have been extensively documented elsewhere⁹.

The UKB Axiom Array contains DNA probes for direct genotyping of the variant underlying the 17bp deletion in *SMIM1* (NC_000001.11:g.3775437_3775453del, rs566629828). The specific DNA probes used (Probeset ID: AX-86577342, Variant ID: Affx-80267180) for detection of the deletion have shown high specificity and the rare variant can be reliably called². For this study, only directly measured genotypes for variant rs566629828 were used to identify UKB participants homozygous for the 17bp

deletion in *SMIM1*, as opposed to imputed genotypes (see below). Additionally, manual inspection of genotype call plots for the deletion probeset (AX-86577342) was performed for each of the 106 genotyping batches of 4,700 UKB samples. The linkage disequilibrium score D' value between variants rs1175550 and rs566629828 was calculated using PLINK software²⁶. The clinical phenotypes have been defined according to the Hospital Episode Statistics (HES) recorded for the majority of UKB participants. The list of ICD-10 codes and fields used to select the cases and traits is in **Table S8**.

NHSBT cohort

All NHSBT blood donors for this study were recruited under approval 12/EE/0040 by the Research Ethics Committee East of England. Initially, the *SMIM1*^{-/-} individuals in the NHSBT cohort of blood donors were identified by the testing approach outlined in an earlier publication⁶. In short, the red cells of a small fraction of the 2 million donations collected annually are tested by haemagglutination for the presence of the Vel blood group antigen with a polyclonal anti-Vel typing reagent. The red cells from donors with a negative result are tested by a confirmatory haemagglutination test using additional anti-Vel typing reagents. If the results of the confirmatory test is again negative then a genotyping test for variant rs566629828 is applied to determine whether the 17bp deletion at rs566629828 is present on both alleles. Currently (December 2021) 141 *SMIM1*^{-/-} donors are registered on NHSBT's donor database (66 females, 75 males). Of these, 25 participated in this study by providing samples and relevant health information obtained during a home visit. 12 of the 25 attended the NIHR Clinical Research Facility at Cambridge University Hospitals (Cambridge, UK) for a 2-day metabolic assessment. The measurement results of the *SMIM1*^{-/-} donors were compared with the results obtained for 180 NHSBT donors (100 females, 80 males) with a reference/reference or reference/alternate genotype for variant rs566629828 as determined by whole-genome sequencing²⁷.

DBDS and CHB cohorts

The CHB participants were recruited under the NVK-1708829, P-2019-93 approval and the DBDS participants were recruited under the 1-10-72-95-13, NVK-1700407, P-2019-99 approval. The CHB participants have been enrolled at the Copenhagen University Hospital and general hospitals in the Zealand region of greater

Copenhagen. Inclusion in the study is limited to patients attending to these hospitals and from whom a blood sample is drawn for ABO and D grouping and/or red cell antibody screening. The cohort is therefore strongly skewed towards patients with medical conditions associated with a high likelihood of requiring transfusion (e.g. surgery, chemotherapy and pregnancy)²¹. The DBDS cohort of Danish blood donors is in demographics similar to the cohort of NHSBT blood donors from whom 25 British *SMIM1*^{-/-} individuals were drawn^{20,28}.

The DNA samples from the 90,000 DBDS and 90,700 CHB participants were genotyped at deCODE Genetics (Reykjavik, Iceland) using the Infinium Global Screening Array (Probeset ID: GSA-24v1-0_C2, v1.0). Imputation of the 17bp deletion rs566629828 was performed by deCODE Genetics using their North European sequencing panel of 15,576 individuals (including 8,429 Danes) as reference. Based on these two imputed datasets, 49 and 34 individuals were identified in DBDS and CHB, with a high likelihood of being homozygous for the 17bp deletion in *SMIM1*, respectively. The DBDS and CHB participant and genotyping data are linked to the Danish Laboratory Database (DLD), the Danish National Patient Registry²⁹ (NPR) and the Danish Prescription Database²⁹ (DPD). These linked databases were used for the association analysis performed for this study.

Confirmation of rs566629828 genotype status

Considering the limited accuracy of imputation to determine the genotype of low-frequency variants, and particularly of indels³⁰, the genotype at rs566629828 was confirmed by an orthogonal test⁷ using DNA extracted from 49 DBDS and 34 CHB blood samples, which were retrieved from the respective sample repositories. In short, DNA was amplified by primers flanking the 17bp deletion in *SMIM1* exon 3 (**Fig.S1**). The amplicons were resolved by agarose gel electrophoresis and visual inspection of the amplicon length (reference and alternate alleles being 178bp and 161bp in length, respectively). Discordant results between the genotype inferred by imputation and the PCR-genotyping test results were observed for 10 DNA samples (DBDS, n=6; CHB, n=4). These ambiguities were resolved by Sanger sequencing of the *SMIM1* coding exons 3 and 4 confirming that all 10 discordances were caused by erroneous imputation results. All together 43 and 30 confirmed *SMIM1*^{-/-} individuals were identified in the DBDS and CHB cohorts, respectively (**Fig.S2**). Controls are drawn

from the same cohorts in a ratio 15:1, gender and age matched (DBDS, n=645; CHB, n=450). The genotype of the controls was imputed and it was either reference/reference or reference/alternate for the variant rs566629828.

Statistical analysis

Linear regression was performed to estimate the effect of continuous variables. The mathematical model used as covariates age, sex and BMI. Where specified, sex and BMI were removed from the equation on occasions. Similarly, for categorical variables, the explanatory effect of variant rs566629828 was estimated by logistic regression. For continuous traits, inverse normal transformation (R package RNOmni) was adopted to normalise the measurements³¹. In the Danish cohorts, the logistic regression analysis was performed with the response variable defined as the presence of an abnormal Nomenclature for Properties and Units (NPU)-code measurement in the DLD dataset, presence of a given ICD10/ICD8 record in the NPR dataset, or presence of a specific prescription in the DPD dataset. The explaining variables used were variant rs566629828 genotype, age of the individuals, genetically inferred sex of the individuals (unless cohort was sex-stratified), and in case of mixed cohort analysis, the cohort of a given individual (DBDS/CHB). Since weight data does not follow a normal distribution, a Wilcoxon signed-rank test was used to assess differences in mean weight-based on variant rs566629828 genotype after sex stratification. Bootstrapping was used to assess directionality in mean weights based on the rs566629828 genotype. For each *SMIM1*^{-/-} DBDS case, 100 alternate age, sex and smoking status matched control groups were picked at random. The mean weight of each of these 100 alternate controls groups was compared to the case group's mean weight. Directionality of the difference in mean weights was then assessed for each sex separately. Statistical tests have P values corrected with Benjamini–Hochberg procedure with alpha set at 0.05.

Metabolic characterisation

The Cambridge Central East of England Research Ethics Committee approved the study protocol for participants' metabolic characterisation (06/Q0108/84). Volunteers were asked to refrain from exercise, consume alcohol and caffeine for 24 hours before arrival. Each of the 12 participants arrived at the NIHR Clinical Research Facility at Cambridge University Hospitals at 14:00 hours on day 0 and remained until noon on

day 1. Resting energy expenditure (REE) was measured upon waking after an overnight fast by indirect calorimetry (GEM Nutrition) using a ventilated hood. Gas analysis exchange measurements were converted into energy equivalents using calculations by Elia and Livesey³². The procedure and precision values of the indirect calorimetry method have been previously described³³. Whole-body fat, lean and bone mass body composition measurements were performed by Dual Energy X-Ray Absorptiometry (DXA). For the volunteers homozygous for the 17bp deletion in *SMIM1*, GE Lunar iDXA (Encore version 18) was used for fat mass, lean mass and bone mineral content (BMC) measurements. For the controls, there was a combination of GE Lunar iDXA measurements and GE Lunar Prodigy measurements (Encore version 16). Therefore, all relevant measurements were converted by cross-calibration equations³⁴ to comparable iDXA values before collating and using regression modelling. Lean mass and REE Z scores were derived by multiple regression modelling¹⁵. The coefficients were updated in line with an upgrade in DXA scanner (REE (kJ/min) = age; -0.015, fat mass (kg); 0.019, lean mass (kg); 0.063, intercept; 1.580, lean mass (kg) = gender (0; male, 1; female); -6.272, height2 (m2); 6.684, bone mass (kg); 10.458, fat mass (kg); 0.166, intercept; 0.888).

Single-cell RNA-seq analyses

We analysed single-cell RNA-sequencing data from the following sources:

- Mouse hypothalamus (GSE113576)¹⁷
- Human fetal pituitary (GSE142653)¹⁸, human in Fig. S3E
- Mouse pituitary (GSE120410)³⁵, mouse in Fig. S3E
- Mouse pituitary (GSE146619)³⁶, mouse in Fig. S3E
- Rat pituitary (GSE132224)³⁷, rat in Fig. S3E
- Mouse thyroid organoids (GSE163818)¹⁹

Normalisation, visualisation, and standard processing of datasets was done through Seurat³⁸. For label transfer of mouse and rat pituitary datasets from the human pituitary reference: mouse and rat genes were first converted to their human homologs (as

obtained via BioMart³⁹), and ambiguously annotated genes were filtered out, prior to cross-species integration.

Mice

C57BL/6N-Smim1^{em2(IMPC)Wtsi}/Wtsi heterozygous mice were obtained from the Wellcome Sanger Institute (Cambridge, UK). Animals were housed in a temperature-controlled room (22°C) with a 12-hour light/dark cycle with 55% relative humidity. Food and water were available *ad libitum*. This research has been regulated under the Animals (Scientific Procedures) Act 1986 Amendment Regulations 2012 following ethical review by the University of Cambridge Animal Welfare and Ethical Review Body (AWERB) and Medical Research Council (MRC) ARES animal facility, under pathogen-free conditions and housed according to UK Home Office guidelines.

Code availability

The code used to analyse the cohorts is available at https://github.com/stefanucci-luca/vel_ko_analysis

Acknowledgements

We would like to thank: all participants in this study, the NIHR Cambridge Clinical Research Facility, the Wellcome Trust-MRC Institute of Metabolic Science Translational Research Facility and the NIHR BioResource. We thank the National Institute for Health Research, NHS Blood and Transplant, and Health Data Research UK as part of the Digital Innovation Hub Programme. L.S. was a PhD student supported by the British Heart Foundation Cambridge Centre for Research Excellence (RE/18/1/34212). S.V. is supported by the British Heart Foundation (RG/18/7/33636). A.V.P. is supported by the British Heart Foundation (RG/18/7/33636) and the Medical Research Council (MRC_MC_UU_12012/5/RCUK). NS and KC are funded by the Wellcome Trust (219496/Z/19/Z & 210755/Z/18/Z). W.H.O. is an NIHR senior investigator and receives funding from the British Heart Foundation, International Society on Thrombosis and Haemostasis, MRC, NIHR and Thermo Fisher Scientific. J.R.S. and M.L.O. are supported by the Swedish Research Council (2019-01683) and governmental university healthcare grants (ALF-4456521). M.L.O. is a Knut and Alice Wallenberg Clinical Scholar (2014.0312, 2020.0234). D.V. is a member of the MRC Centre for Environment and Health, currently funded by the Medical Research Council

(MR/S019669/1, 2019-2024). M.F. is supported by the British Heart Foundation (FS/18/53/33863) and the British Heart Foundation Cambridge Centre for Research Excellence (RE/18/1/34212).

Authors contribution

L.S. and C.M. analysed data and wrote the manuscript. A.R.T. collected samples and performed the mouse work. S.V. performed the mouse work. N.S.G. analysed data and reviewed the genotype calls. L.P.E.W. supervised clinical research facility data collection and analysed data. J.E.K. analysed single cell datasets. F.B and S.F. collected samples. J.C. analysed the glucose level data. U.V. analysed the eQTL data. K.B. and P.B. supervised the plasma biochemistry assays. J.W. performed histopathology. L.W., J.O., A.F., K.R., S.E.A., J.P., G.B. and H.J. organised and performed the NHSBT donors recruitment and sample collection. W.N.E. and G.J.H. analysed the pathology samples. N.S. provided advice for the mouse work and data interpretation. C.E., K.R., M.D. and H.U. supervised the establishment of the Danish cohort. A.S. analysed the clinical research facility data. K.S. supervised the genotyping of the Danish cohorts. V.A. and M.V. provided advice with data interpretation. O.A.B. supervised single cell RNA sequencing data analysis. A.V.P. supervised mouse work. S.R.O. supervised the Danish cohorts analysis. W.J.A. provided statistical analysis supervision. J.R.S. helped with the Danish cohort genotyping validation and advised on analysis. M.L.O., O.B.P. and W.H.O. provided supervision, planned analyses, contributed to data interpretation and wrote the manuscript. K.C. supervised the clinical research facility metabolic characterisation. D.V. provided statistical analysis supervision. M.F. was responsible for project organisation, funds, supervision, experimental and analysis planning, and wrote the manuscript. All authors approved the final version of the manuscript.

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495 databases and microarray data analysis. *Bioinformatics* **21**, 3439–3440 (2005).

496 Tables index

- 497 Table S1 | **Linear regression outcomes in the UKB cohort for the traits of interest.**
 498 This table contains the trait tested (feature) and the effect size (effect) of *SMIM1* *-/-* on
 499 each trait. Standard deviation (sd); confidence intervals (CI); p.value corrected with
 500 the Benjamini-Hochberg procedure (p.val.FDR). The Tabs contains the values for the
 501 effect not corrected for BMI (no BMI correction) and corrected for the effect of BMI on
 502 the traits of interest (BMI corrected). Also, the cohort was stratified by sex and the
 503 different results for the strata have been reported in different tabs. Tabs with “sex”
 504 label refer to the analysis that uses the whole cohort (i.e. not sex-stratified), but
 505 corrected for the effect of sex. On the first tab of this table there is a short demographic
 506 description of the UKB cohort, *SMIM1* *-/-* and *SMIM1* *+/+* used for this study
- 507 Table S2 | **Mice raw data.** Characteristics of the *Smim1* *-/-* and *+/+* littermates used
 508 in Fig.1D.
- 509 Table S3 | **Raw data collected in the NHSBT cohort.** The first tab has the cohort
 510 characteristics and biochemistry raw data collected from the NHSBT cohort. Body
 511 mass index (BMI), leptin to adiponectin ratio (LAR), cholesterol (CHOL), triglycerides
 512 levels (TG), high-density lipoprotein (HDL), alanine aminotransferase (ALT), leptin
 513 (LEPT), adiponectin (ADPN), aspartate aminotransferase (AST), C reactive protein
 514 (hsCRP), free fatty acids (FFA), thyroid-stimulating hormone (TSH), low-density
 515 lipoproteins (LDL), triiodothyronine (T3), thyroxine (T4). The second tab has the free
 516 T3 and free T4 measurements for a subset of the cohort.
- 517 Table S4 | **Linear regression outcomes in the NHSBT cohort for the traits**
 518 **presented in Table S3.** It contains the trait tested (feature) and the effect size (effect)
 519 of *SMIM1* *-/-* on each trait. Standard deviation (sd); confidence intervals (CI); p.value
 520 corrected with the Benjamini-Hochberg procedure (p.val.FDR). The Tabs contains the
 521 values for the effect not corrected for BMI (no BMI correction) and corrected for the
 522 effect of BMI on the traits of interest (BMI corrected). Also, the cohort was stratified by
 523 sex and the different results for the strata have been reported in different tabs. Tabs
 524 with “sex” label refers to the analysis that uses the whole cohort (i.e. not gender
 525 stratified) but corrected for the effect of gender.

Table S5 | Resting energy expenditure (REE) raw data in the NHSBT cohort. lean mass (LM). Both REE and LM have been reported as Z scores.

Table S6 | Statistical analysis in the DBDS and CHB cohorts. (cohort tab) Characteristics data for DBDS and CHB cohorts. (Weight male/female tabs) Test for differences in average weight based on *SMIM1* genotypes. (NPR not sex-stratified, male and female tabs) Logistic regression of the effect of *SMIM1* genotype on the diagnosis of Ischaemic heart disease, Hyperthyroidism, Diabetes and Obesity. (DPD tab) Logistic regression for the effect of *SMIM1* genotypes on prescriptions for Cardiovascular disease, Hypertension, Diabetes and Metabolism. (ICD10) and (ICD8) International Classification of Diseases diagnosis code groups. (p.val) p.value, (glm_OR) Odds ratio, (CI_high) and (CI_low) 95% confidence intervals, (N.total.pos) and (N.total.neg) total number of *SMIM1*+ positive and *SMIM1*-/- in a given analysis. (N.prescription.pos) and (N.prescription.neg) the total number of individuals with or without a given prescription in a given analysis. (N.diag.pos) and (N.diag.neg) the total number of individuals with or without a given diagnosis in a given analysis. (gender) genders included in a given analysis. (covariates) the covariates included in a given analysis. (N male) and (N female) number of males or females in each cohort, (age male) and (age female) average age of the males or females in each cohort. (sex-fraction) fraction of females to males in a given cohort. (mean *SMIM1*+) and (mean *SMIM1*-/-) the mean weight of each *SMIM1* genotype group. (cohort) the cohort affiliation of a data point or analysis, either DBDS, CHB or both. (p.val wilcoxon) p.value of Wilcoxon signed-rank test for a difference in mean weight between the DBDS *SMIM1* genotype groups. (feature) The general condition type being investigated. (prescriptions) The types of prescriptions grouped in the analysis. (ATC) the ATC classification codes of each prescription group.

Table S7 | Generalised linear regression in the UKB cohort for the diseases of interest. This table contains the disease tested (Disease) and the effect size (effect (OR)) of *SMIM1*-/- on each trait. Odds ratio (OR); standard deviation (sd); confidence intervals (CI); p.value corrected with the Benjamini-Hochberg procedure (p.val.FDR). Disease traits have been defined according to the HES and ICD-10 codes reported in Table S9. The effect of the *SMIM1*-/- have been corrected for the BMI (tab "Corrected for BMI")

558 Table S8 | **UKB fields and phenotype definitions used in the analysis of the UKB**
559 **cohort.** The tab “Fields extracted from UKB” contains the list of fields that have been
560 used in the characterisation of the UKB cohort. The tab “matrix_ICD10_Phenotype”
561 contains the information regarding the ICD-10 codes that have been used to define a
562 disease.

Fig.1

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Fig.1 | **Differences between *SMIM1*^{+/+} and *SMIM1*^{-/-} individuals in the UKB cohort and *Smim1*^{-/-} knockout mice.** (A) Box plots for UKB participants weight (kg) grouped according to their genotype. Sex-stratified data have are shown for the three genotype groups, with females on the left and males on the right, respectively. Boxplot whiskers indicate the 95% confidence interval. (B) Box plots for BMI, waist circumference, and levels of triglycerides (TG), alanine aminotransferase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (GGT) and urate. Boxplot whiskers indicate the 95% confidence interval. (C) Forest plot illustrating the effect size ($\hat{\beta}$; percentage of standard deviation) of *SMIM1*^{+/+} (blue) versus *SMIM1*^{-/-} (red) for each trait. Bold characters highlight the measurements that are shown in panel B. Effect sizes corrected for BMI are shown in yellow, and the none corrected ones are in dark grey; β is represented by the dot and the 95% confidence intervals by the horizontal line. (D) Weight trajectories (weight in grams, y-axis; age in weeks, x-axis) comparison between WT (blue) and *Smim1* knockout littermates (red), with females (left) and males (right).

Fig.2

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Fig.2 | **Differences between *SMIM1*^{+/+} and *SMIM1*^{-/-} individuals in the NHSBT cohort and DXA body scan.** (A) Boxplots for free fatty acids (FFA), ALT, AST, ferritin, leptin to adiponectin ratio (LAR), total triiodothyronine (T3), total thyroxine (T4). Boxplot whiskers indicate the 95% confidence interval. (B) Forest plot illustrating the effect size ($\hat{\beta}$; percentage of standard deviation) of *SMIM1*^{+/+} versus *SMIM1*^{-/-} for each trait. Effect sizes corrected for BMI and non-corrected ones are in yellow and dark grey, respectively. β is represented by the dot and the 95% confidence intervals by the horizontal line. (C) Scatter plot of Z-scores for resting energy expenditure (REE; x-axis) and lean mass (LM; y-axis). *SMIM1*⁺ individuals, teal; *SMIM1*^{-/-} individuals, red. The three *SMIM1*^{-/-} individuals shown in Fig.2D are indicated by the black dots with a red circumference. (D) Representative DXA scans showing fat volume and distribution in three *SMIM1*⁺ participants from the control group (top row, teal borders) and three participants from the *SMIM1*^{-/-} group (bottom row, red borders).

B

C

Fig.S1 | **Associations with red blood cell distribution width at the *SMIM1* locus.**

(A) Upper panel: *SMIM1* is localised on chromosome 1 at Chr1:p36.23. Middle panel: The genomic region harbouring the *SMIM1* gene between coordinates chr1:3,772,749-3,775,982 with the four grey boxes representing the *SMIM1* exons, the grey lines being the introns and the arrows in the introns giving the transcript direction. The bright green and red vertical arrows indicate the position of the eQTL variant rs1175550 with an A and G nucleotide being reference and alternate, respectively and of the deletion variant rs566629828 with a reference containing the 17bp sequence of GTCAGCCTAGGGGCTGT and the alternate lacking this sequence, respectively. The distance in base pairs (bp) and the D' value between the two variants are presented above and below the bidirectional horizontal arrow. Lower panel: The predicted sequence of the 78-amino acid (in single letter code) type II *SMIM1* protein, with an estimated seven amino acids for the extracellular domain (purple), 23-amino acids for the transmembrane domain (light green) and with the remaining 48-amino acids being cytoplasmic (dark green). The asterisk indicates, on the protein, where the frame changes because of the deletion. (B) Locus zoom plots for *SMIM1* (highlighted in green) genomic region showing the 100,000 bp centred on variant rs566629828; the normalised $-\log_{10}$ P-values for the association between variants and red cell distribution width (RDW) are on the y-axis. The sentinel variant rs1175550 (eQTL variant in blood) is in green; after conditional analysis, it was observed that the 17bp deletion (rs566629828, indicated in red) was independent of the sentinel variant associated with RDW. (C) Effect of the *SMIM1* rs1175550 eQTL variant and rs566629828 (17bp deletion) genotypes onto normalised RDW. The two boxplots have RDW distribution (y-axis) by genotype (x-axis). rs1175550 has ref/ref (A/A) in the darkest green, ref/alt (A/G) in green and alt/alt (G/G) in the lightest of green; rs566629828 have *SMIM1*+/+ in blue, *SMIM1*+/- in orange and *SMIM1*-/- in red. The beta and P-values for the associations are given above the boxplots, note the opposing directionality of the beta values, being negative for the eQTL variant (in blood *SMIM1*+/+ transcript level in alt/alt > alt/ref > ref/ref) and being positive for the deletion variant. This is in keeping with the observation that lower levels of *SMIM1* RNA are associated with higher RDW levels. It is also worthwhile noting that in red cells effects of the eQTL and the 17bp deletion variants are also observed in heterozygous individuals - this is in sharp contrast with the effect of the 17bp deletion on body weight (Fig.1A).

625 Fig.S2 | **Cohort information and the number of *SMIM1*^{-/-} individuals per cohort**

626 Genotype and phenotype data from four cohorts were used for the study. From left to
627 right UK Biobank (UKB), National Health Service Blood and Transplant (NHSBT),
628 Danish Blood Donor Study (DBDS and The Copenhagen Hospital Biobank (CHB). The
629 top row provides the number of participants for whom genotype (Vel phenotype in case
630 of NHSBT cohort) information was available and the female:male ratio. For the UKB
631 the ethnicity of the participants is also provided (data taken from Bycroft *et al.*, 2018)¹⁰.
632 The middle row provides the number of *SMIM1*^{-/-} individuals per cohort which were
633 included in the study; between brackets (female/male) individuals.

A Fig.S3

B

C

D

E

F

Fig.S3 | ***SMIM1* expression at single-cell resolution in mammalian hypothalamus, pituitary and thyroid.** (A) UMAP representation of the different cell types found in mouse hypothalamus snRNA-seq data (GSE113576). (B) *Smim1* and *Trh* expression levels in the different cell types found in mouse hypothalamus. (C) UMAP representation of the different cell types found in human foetal pituitary scRNA-seq data (GSE142653). (D) *SMIM1* and representative genes expression levels in the different cell types found in the human foetal pituitary. (E) *Smim1* and representative genes expression levels in the different cell types found in rat and mouse pituitary. (F) *Smim1* and representative genes expression levels in the different cell types found in mouse thyroid organoids (GSE163818).

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