



**University of Dundee**

## **The trans-ancestral genomic architecture of glyceemic traits**

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## The Trans-Ancestral Genomic Architecture of Glycemic Traits

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458

459

460

461 **Abstract**

462 Glycemic traits are used to diagnose and monitor type 2 diabetes, and cardiometabolic health. To  
463 date, most genetic studies of glycemic traits have focused on individuals of European ancestry. Here,  
464 we aggregated genome-wide association studies in up to 281,416 individuals without diabetes (30%  
465 non-European ancestry) with fasting glucose, 2h-glucose post-challenge, glycated hemoglobin, and  
466 fasting insulin data. Trans-ancestry and single-ancestry meta-analyses identified 242 loci (99 novel;  
467  $P < 5 \times 10^{-8}$ ), 80% with no significant evidence of between-ancestry heterogeneity. Analyses restricted  
468 to European ancestry individuals with equivalent sample size would have led to 24 fewer new loci.  
469 Compared to single-ancestry, equivalent sized trans-ancestry fine-mapping reduced the number of  
470 estimated variants in 99% credible sets by a median of 37.5%. Genomic feature, gene-expression  
471 and gene-set analyses revealed distinct biological signatures for each trait, highlighting different  
472 underlying biological pathways. Our results increase understanding of diabetes pathophysiology by  
473 use of trans-ancestry studies for improved power and resolution.

474 Fasting glucose (FG), 2h-glucose post-challenge (2hGlu), and glycated hemoglobin (HbA1c) are  
475 glycemic traits used to diagnose diabetes<sup>1</sup>. In addition, HbA1c is the most commonly used biomarker  
476 to monitor glucose control in patients with diabetes. Fasting insulin (FI) reflects a combination of  
477 insulin secretion and insulin resistance, both components of type 2 diabetes (T2D), and insulin  
478 clearance<sup>2</sup>. Collectively, all four glycemic traits can be useful to better understand T2D  
479 pathophysiology<sup>3-5</sup> and cardiometabolic outcomes<sup>6</sup>.

480

481 To date, genome-wide association studies (GWAS) and analysis of MetaboChip and exome arrays  
482 have identified >120 loci associated with glycemic traits in individuals without diabetes<sup>7-15</sup>. However,  
483 despite considerable differences in the prevalence of T2D risk factors across ancestries<sup>16-18</sup>, most  
484 glycemic trait GWAS have insufficient representation of individuals of non-European ancestry and  
485 limited resolution for fine-mapping of causal variants and effector transcript identification. Here, we  
486 present large-scale trans-ancestry meta-analyses of GWAS for four glycemic traits in individuals  
487 without diabetes. We aimed to identify additional glycemic trait-associated loci; investigate the  
488 portability of loci and genetic scores across ancestries; leverage differences in effect allele frequency  
489 (EAF), effect size, and linkage disequilibrium (LD) across diverse populations to conduct fine-mapping  
490 and aid causal variant/effector transcript identification; and compare the genetic architecture of  
491 glycemic traits to further elucidate underlying biology and T2D pathophysiology.

492

## 493 Results

### 494 Study design and definitions

495 To identify loci associated with glycemic traits FG, 2hGlu, FI, and HbA1c, we aggregated GWAS in up  
496 to 281,416 individuals without diabetes, ~30% of whom were of non-European ancestry [13% East  
497 Asian, 7% Hispanic, 6% African-American, 3% South Asian, and 2% sub-Saharan African (Ugandan  
498 data only available for HbA1c)]. Each cohort imputed data to the 1000 Genomes Project reference  
499 panel<sup>19</sup> (phase 1 v3, March 2012, or later; **Methods, Supplementary Table 1, Extended Data Figure  
500 1, Supplementary Note**). Up to ~49.3 million variants were directly genotyped or imputed, with  
501 between 38.6 million (2hGlu) and 43.5 million variants (HbA1c) available for analysis after exclusions  
502 based on minor allele count (MAC < 3) and imputation quality (imputation  $r^2$  or INFO score < 0.40) in  
503 each cohort. FG, 2hGlu and FI analyses were adjusted for BMI<sup>15</sup> but for simplicity they are  
504 abbreviated as FG, 2hGlu and FI (**Methods**).

505

506 We first performed trait-specific fixed-effect meta-analyses *within* each ancestry using METAL<sup>20</sup>. We  
507 defined “single-ancestry lead” variants as the strongest trait-associated variants ( $P < 5 \times 10^{-8}$ ) within a  
508 1Mb region in an ancestry (**Table 1**). Within each ancestry and each chromosome, we used approximate  
509 conditional analyses in GCTA<sup>21,22</sup>, to identify “single-ancestry index variants” ( $P < 5 \times 10^{-8}$ ) that exert  
510 conditionally distinct effects on the trait (**Table 1, Methods, Supplementary Note**). This approach  
511 identified 124 FG, 15 2hGlu, 48 FI and 139 HbA1c variants that were significant in at least one  
512 ancestry (**Supplementary Table 2**).

513

514 Next, we conducted trait-specific *trans-ancestry* meta-analyses using MANTRA (**Methods,  
515 Supplementary Table 1, Supplementary Note**) to identify genome-wide significant “trans-ancestry  
516 lead variants”, defined as the most significant trait-associated variant across all ancestries ( $\log_{10}$   
517 Bayes Factor [BF] > 6, equivalent to  $P < 5 \times 10^{-8}$ )<sup>23</sup> (**Table 1, Methods**). Here, we present trans-ancestry  
518 results as our primary results (**Supplementary Table 2**).

519

520 Causal variants are expected to affect related glycemic traits and may be shared across ancestries.  
521 Therefore, we combined all single-ancestry lead variants, single-ancestry index variants, and/or  
522 trans-ancestry lead variants (for any trait) mapping within 500Kb of each other, into a single “trans-  
523 ancestry locus” bounded by 500Kb flanking sequences (**Table 1, Extended Data Figure 2**). As defined,

524 a trans-ancestry locus may contain multiple causal variants affecting one or more glycemic traits,  
525 exerting their effect in one or more ancestry.

526

### 527 **Glycemic trait locus discovery**

528 Trans-ancestry meta-analyses identified 235 trans-ancestry loci, of which 59 contained lead variants  
529 for more than one trait. In addition, we identified seven “single-ancestry loci” that did not contain  
530 any trans-ancestry lead variants (**Table 1, Supplementary Table 2**). Of the 242 combined loci, 99  
531 (including 6 of the 7 single-ancestry) had not been previously associated with any of the four  
532 glycemic traits or with T2D, at the time of analysis (**Figure 1, Supplementary Table 3, Supplementary**  
533 **note**). However, based on recent East Asian and trans-ancestry T2D GWAS meta-analyses<sup>23-27</sup>, the  
534 lead variants at 27/99 novel glycemic trait loci have strong evidence of association with T2D ( $P < 10^{-4}$ ;  
535 13 loci with  $P < 5 \times 10^{-8}$ ), suggesting they are also important in T2D pathophysiology (**Supplementary**  
536 **Tables 2 and 4**).

537

538 Of the six single-ancestry novel loci, three were unique to non-European ancestry individuals  
539 (**Supplementary Table 3**). An African American association for FI (lead variant rs12056334) near  
540 *LOC100128993* (an uncharacterized RNA gene; **Supplementary Note**). An African American  
541 association for FG (lead variant rs61909476) near *ETS1* and a Hispanic association for FG (lead  
542 variant rs12315677) within *PIK3C2G* (**Supplementary Table 3**). Despite broadly similar EAF across  
543 ancestries, rs61909476 was only significantly associated with FG in African American individuals (EAF  
544 ~7%,  $b = 0.0812$  mmol/l,  $SE = 0.01$  mmol/l,  $P = 3.9 \times 10^{-8}$  vs EAF 10-17%,  $b = 0.002$  mmol/l,  $se = 0.003$ -  
545  $0.017$  mmol/l,  $P = 0.44$ - $0.95$  in all other ancestries, **Supplementary table 2, Supplementary note**). The  
546 nearest gene, *ETS1*, encodes a transcription factor that localizes to insulin-positive cells, and its  
547 overexpression decreases glucose-stimulated insulin secretion in mouse islets<sup>28</sup>. Located within the  
548 *PIK3C2G* gene, rs12315677 has an 84% EAF in Hispanic (70-94% in other ancestries) and is only  
549 significantly associated with FG in this ancestry ( $b = 0.0387$  mmol/l,  $SE = 0.0075$  mmol/l,  $P = 4.0 \times 10^{-8}$  vs  
550  $b = -0.0128$ - $0.010$  mmol/l,  $SE = 0.003$ - $0.018$  mmol/l,  $P = 0.14$ - $0.76$  in all other ancestries,  
551 **Supplementary note**). In mice, deletion of *Pik3c2g* leads to a phenotype characterized by reduced  
552 glycogen storage in the liver, hyperlipidemia, adiposity, and insulin resistance with increasing age, or  
553 after a high fat diet<sup>29</sup>. Instances of similar EAFs but differing effect sizes between populations, could  
554 be due to genotype-by-environment or other epistatic effects. Alternatively, lower imputation  
555 accuracy in smaller sample sizes could deflate effect sizes, although imputation quality for these  
556 variants was good (average  $r^2 = 0.81$ ). Finally, the variants detected here may be in LD with ancestry-  
557 specific causal variants not interrogated here that differ in frequency across ancestries. However, we  
558 could not find evidence of rarer alleles in the cognate populations from the 1000G project  
559 (**Supplementary Table 5**). The final three single-ancestry loci were identified in individuals of  
560 European ancestry (**Supplementary note**).

561

562 Next, by rescaling the standard errors of allelic effect sizes to artificially boost the sample size of the  
563 European meta-analysis to match that of trans-ancestry meta-analysis, we determined that 21 of the  
564 novel trans-ancestry loci would not have been discovered with an equivalent sample size comprised  
565 exclusively of European ancestry individuals (**Supplementary note**). Their discovery was due to the  
566 higher EAF and/or larger effect size in non-European ancestry populations. In particular, two loci  
567 (near *LINC00885* and *MIR4278*) contain East Asian and African American single-ancestry lead  
568 variants, respectively, suggesting that these specific ancestries may be driving the trans-ancestry  
569 discovery (**Supplementary Tables 2-3**). Combined with the three single-ancestry non-European loci  
570 described above, our results show that 24% (24/99) of novel loci were discovered due to the  
571 contribution of non-European ancestry participants, strengthening the argument for expanding  
572 genetic studies in diverse populations.

573

### 574 **Allelic architecture of glycemic traits**

575 Single-ancestry and trans-ancestry results combined increased the number of established loci for FG  
576 to 102 (182 signals, 53 novel loci), FI to 66 (95 signals, 49 novel loci), 2hGlu to 21 (28 signals, 11  
577 novel loci), and HbA1c to 127 (218 signals, 62 novel loci) (**Supplementary Table 2**), with significant  
578 overlap across traits (**Extended Data Figure 3**). We also detected ( $P < 0.05$  or  $\log_{10}BF > 0$ ) the vast  
579 majority (~90%) of previously established glycemic signals, 70-88% of which attained genome-wide  
580 significance (**Supplementary Note, Supplementary Table 6**). Given that analyses for FG, FI, and  
581 2hGlu were performed adjusted for BMI, we confirmed that collider bias did not influence >98% of  
582 signals discovered (**Supplementary note**)<sup>31</sup>. As expected, given the greater power due to increased  
583 sample sizes, new association signals tended to have smaller effect sizes and/or EAFs in European  
584 ancestry individuals compared to established signals (**Extended Data Figure 4**).

585

#### 586 **Characterization of lead variants across ancestries**

587 To better understand the transferability of trans-ancestry lead variants across ancestries, we  
588 investigated the pairwise EAF correlation and the pairwise summarized heterogeneity of effect sizes  
589 between ancestries<sup>32</sup> (**Methods, Supplementary Note**). Consistent with population history and  
590 evolution, these results demonstrated considerable EAF correlation ( $\rho^2 > 0.70$ ) between European  
591 and Hispanic, European and South Asian, and Hispanic and South Asian populations, consistent  
592 across all four traits, and between African Americans and Ugandans for HbA1c (**Extended Data**  
593 **Figure 5**). Despite significant EAF correlations, some pairwise comparisons exhibited strong evidence  
594 for effect size heterogeneity between ancestries that was less consistent between traits (**Extended**  
595 **Data Figure 5**). However, sensitivity analyses demonstrated that, across all comparisons, the  
596 evidence for heterogeneity is driven by a small number of variants, with between 81.5% (for HbA1c)  
597 and 85.7% of trans-ancestry lead variants (for FG) showing no evidence for trans-ancestry  
598 heterogeneity ( $P > 0.05$ ) (**Supplementary Note**).

599

#### 600 **Trait variance explained by associated loci**

601 The trait variance explained by genome-wide significant loci was assessed using the single-ancestry  
602 variants only or a combination of single-ancestry and trans-ancestry variants (**Supplementary Table**  
603 **7**) with betas extracted from the relevant single-ancestry meta-analysis results (**Methods**). The  
604 variance explained was assessed by linear regression in a subset of the contributing cohorts  
605 (**Methods, Supplementary Tables 8-11**). In general, the approach that explained the most variance  
606 was to begin with the trans-ancestry lead variants that had  $P < 0.1$  in the relevant single-ancestry  
607 meta-analysis, then add in all single-ancestry variants that were not in LD with the trans-ancestry  
608 variants ( $LD\ r^2 < 0.1$ ) (List C, **Supplementary Tables 8-11, Figure 2**). Using this approach, the mean  
609 variance in the trait distribution explained was between 0.7% (2hGlu in EUR) and 6% (HbA1c in AA).  
610 The European-based estimates explained more variance relative to previous estimates of 2.8% for  
611 FG and 1.7% for HbA1c<sup>33</sup> (**Supplementary Note**).

612

#### 613 **Transferability of EUR ancestry-derived polygenic scores**

614 To investigate the transferability of polygenic scores across ancestries we used the PRS-CSauto  
615 software<sup>34</sup> to first build polygenic scores for each glycemic trait based on European ancestry data.  
616 However, the training set for 2hGlu was too small so this trait was excluded. To build the polygenic  
617 scores (PGS), for each trait we first removed five of the largest European cohorts from the European  
618 ancestry meta-analysis. These five cohorts were meta-analyzed and used as our European ancestry  
619 test dataset, for each trait. The remaining European ancestry cohorts were also meta-analyzed and  
620 used as the training dataset, from which we derived a PGS for each trait (**Methods**). We used PRS-  
621 CSauto to revise the effect size estimates for the variants in the score (obtained from the training  
622 European datasets) based on the LD of the test population. PRS-CSauto does not have LD reference  
623 panels for South Asian or Hispanic ancestry and as such we were unable to test the transferability of  
624 the PGS into those populations. The “gtx” package<sup>35</sup> (**Methods**) was used to obtain the  $R^2$  for each  
625 test population (**Figure 3, Supplementary Table 12**). Consistent with other complex traits<sup>36</sup>, the

626 European ancestry-derived PGS had greater predictive power into test data of European ancestry  
627 than other ancestry groups.

628

### 629 **Fine-mapping**

630 We fine-mapped, 231 trans-ancestry and six single-ancestry autosomal loci (**Supplementary Table 2,**  
631 **Supplementary note**). Using FINEMAP with ancestry-specific LD and an average LD matrix across  
632 ancestries, we conducted fine-mapping both within (161 loci with single-ancestry lead variants) and  
633 across ancestries (231 loci) for each trait (**Methods**). Because 59 of the 231 trans-ancestry loci were  
634 associated with more than one trait, we conducted trans-ancestry fine-mapping for a total of 305  
635 locus-trait associations. Of these 305 locus-trait combinations, FINEMAP estimated the presence of a  
636 single causal variant at 186 loci (61%), while multiple distinct causal variants were implicated at 126  
637 loci (39%), for a total of 464 causal variants (**Figure 4A**).

638

### 639 *Credible sets for causal variants*

640 At each locus, we next constructed credible sets (CS) for each causal variant that account for  $\geq 99\%$   
641 of the posterior probability of association (PPA). We identified 21 locus-trait associations (at 19 loci)  
642 for which the 99% CS included a single variant, and we highlight four examples (**Methods,**  
643 **Supplementary Note, Figure 4B, Supplementary Table 13**).

644

645 At *MTNR1B* and *SIX3* we identified, respectively, rs10830963 (PPA>0.999, for both HbA1c and FG)  
646 and rs12712928 (PPA=0.997, for FG) as the likely causal variants. At both loci previous studies  
647 confirm these variants affect transcriptional activity<sup>37,38,39</sup> (**Supplementary note**). At a locus near  
648 *PFKM* associated with HbA1c, trans-ancestry fine-mapping identified rs12819124 (PPA>0.999) as the  
649 likely causal variant. This variant has been previously associated with mean corpuscular  
650 hemoglobin<sup>40</sup>, suggesting an effect on HbA1c via the red blood cell (RBC, **Supplementary note**). At  
651 *HBB*, we identified rs334 (PPA>0.999; Glu7Val) as the likely causal variant associated with HbA1c.  
652 rs334 is a causal variant of sickle cell anemia<sup>41</sup>, previously associated with urinary albumin-to-  
653 creatinine ratio in Caribbean Hispanic individuals<sup>42</sup>, severe malaria in a Tanzanian study population<sup>43</sup>,  
654 hematocrit and mean corpuscular volume in Hispanic/Latino populations<sup>44</sup>, and RBC distribution in  
655 Ugandan individuals<sup>45</sup>, all pointing to a variant effect on HbA1c via non-glycemic pathways.

656

657 The remaining locus-trait associations with a single variant in the 99% CS (**Supplementary Table 13**)  
658 point to variants that could be prioritized for functional follow-up to elucidate impact on glycemic  
659 trait physiology.

660

661 At an additional 156 locus-trait associations trans-ancestry fine-mapping identified 99% CS with 50  
662 or fewer variants (**Figure 4B, Supplementary Table 13**). Consistent with the potential for >1 causal  
663 variant in a locus, 74 locus-trait associations contained 88 variants with PPA>0.90 that are strong  
664 candidate causal variants (**Supplementary Table 14**). For example, 10 are coding variants including  
665 several missense such as the *HBB* Glu7Val mentioned above, *GCKR* Leu446Pro, *RREB1* Asp1771Asn,  
666 *G6PC2* Pro324Ser, *GLP1R* Ala316Thr, and *TMPRSS6* Val736Ala, each of which have been proposed or  
667 shown to affect gene function<sup>12,46-50</sup>. We additionally identified *AMPD3* Val311Leu (PPA=0.989) and  
668 *TMC6* Trp125Arg (PPA>0.999) variants associated with HbA1c which were previously detected in an  
669 exome array analysis but had not been fine-mapped with certainty due to the absence of backbone  
670 GWAS data<sup>30</sup>. Our fine-mapping now suggest these variants are likely causal and identify their  
671 cognate genes as effector transcripts.

672

673 Finally, we evaluated the resolution obtained in the trans-ancestry versus single-ancestry fine-  
674 mapping (**Methods, Supplementary Note**). We compared the number of variants in 99% CS across  
675 98 locus-trait associations which, as suggested by FINEMAP, had a single causal variant in both trans-  
676 ancestry and single-ancestry analyses. Fine-mapping within and across ancestries was conducted

677 using the same set of variants. At 8 of 98 locus-trait associations single-ancestry fine-mapping  
678 identified a single variant in the CS. In addition, at 72 of the 98 locus-trait associations, the number  
679 of variants in the 99% CS was smaller in the trans-ancestry fine-mapping (**Figure 4C**), which likely  
680 reflects the larger sample size and differences in LD structure, EAFs, and effect sizes across diverse  
681 populations. To quantify the estimated improvement in fine-mapping resolution attributable to the  
682 multi-ancestry GWAS, we then compared 99% CS sizes from the trans-ancestry fine-mapping to  
683 single-ancestry-specific data emulating the same total sample size by rescaling the standard errors  
684 (**Methods**). Of the 72 locus-trait associations with estimated improved fine-mapping in trans-  
685 ancestry analysis, resolution at 38 (53%) was improved because of the larger sample size in the  
686 trans-ancestry fine-mapping analysis (**Figure 4C**), and this estimated improved resolution would  
687 likely have been obtained in a European-only fine-mapping effort with equivalent sample size.  
688 However, at 34 (47%) loci, the inclusion of samples from multiple diverse populations yielded the  
689 estimated improved resolution. On average, ancestry differences led to a reduction in the median  
690 number of variants in the 99% CS from 24 to 15 variants (37.5% median reduction; **Figure 4C**),  
691 demonstrating the value of conducting fine-mapping across ancestries.

692

### 693 **HbA1c Signal Classification**

694 HbA1c-associated variants can exert their effects on HbA1c levels through both glycemc and non-  
695 glycemc pathways<sup>7,51</sup> and their correct classification can affect T2D diagnostic accuracy<sup>7,52</sup>. Using  
696 prior association results for other glycemc, RBC, and iron traits, and a fuzzy clustering approach we  
697 classified variants into their most likely mode of action (**Methods, Supplementary note**). Of the 218  
698 HbA1c-associated variants, 27 (12%) could not be characterized due to missing data and 23 (11%)  
699 could not be classified into a “known” class (**Supplementary note**). The remaining signals were  
700 classified as principally: a) glycemc (n=53; 24%), b) affecting iron levels/metabolism (n=12; 6%), or c)  
701 RBC traits (n=103; 47%). A genetic risk score (GRS) composed of all HbA1c-associated signals was  
702 strongly associated with T2D risk (OR=2.4, 95% CI 2.3-2.5,  $P=2.7 \times 10^{-298}$ ). However, when using  
703 partitioned GRSs composed of these different classes of variants (**Methods**), we found the T2D  
704 association was mainly driven by variants influencing HbA1c through glycemc pathways (OR=2.6,  
705 95% CI 2.5-2.8,  $P=2.3 \times 10^{-250}$ ), with weaker evidence of association (despite the larger number of  
706 variants in the GRS) and a more modest risk (OR=1.4, 95% CI 1.2-1.7,  $P=4.7 \times 10^{-4}$ ) imparted by signals  
707 in the mature RBC cluster that were not glycemc (i.e. where those specific variants had  $P>0.05$  for  
708 FI, 2hGlu and FG) (**Extended Data Figure 6, Supplementary note**). This contrasts our previous finding  
709 where we found no significant association between a risk score of non-glycemc variants and T2D<sup>7</sup>.  
710 Our current results could be partly driven by T2D cases being diagnosed based on HbA1c levels that  
711 may be influenced by the non-glycemc signals, or by glycemc effects not captured by FI, 2hGlu or  
712 FG measures.

713

### 714 **Biological signatures of glycemc trait associated loci**

715 To better understand distinct and shared biological signatures underlying variant-trait associations,  
716 we conducted genomic feature enrichment, eQTL co-localization, and tissue and gene-set  
717 enrichment analyses across all four traits.

718

### 719 **Epigenomic landscape of trait-associated variants**

720 We explored the genomic context underlying glycemc trait loci by computing overlap enrichment  
721 for annotations such as coding, conserved regions, and super enhancers merged across multiple cell  
722 types<sup>53-55</sup> using the GREGOR tool<sup>56</sup>. We observed that FG, FI and HbA1c signals (**Supplementary**  
723 **Table 7**) were significantly ( $P<8.4 \times 10^{-4}$ , Bonferroni threshold for 59 annotations) enriched in  
724 evolutionarily conserved regions (**Fig 5A, Extended Data Figure 7, Supplementary Table 15**).



725  
726 We then considered epigenomic landscapes defined in individual cell/tissue types. Previously,  
727 stretch enhancers (StrE, enhancer chromatin states  $\geq 3\text{kb}$  in length) in pancreatic islets were shown  
728 to be highly cell-specific and strongly enriched with T2D risk signals<sup>57</sup>. Considering StrEs across 31  
729 cell-types<sup>39</sup>, FG and 2hGlu signals showed the highest enrichment in islets (FG: fold-  
730 enrichment=4.70,  $P=2.7 \times 10^{-24}$ ; 2hGlu: fold-enrichment=5.51,  $P=3.6 \times 10^{-4}$  **Figure 5A, Supplementary**  
731 **Table 16**), highlighting the importance of islets for these traits. FI signals were enriched in skeletal  
732 muscle (fold-enrichment=3.17,  $P=7.8 \times 10^{-6}$ ) and adipose StrEs (fold-enrichment=3.27,  $P=1.8 \times 10^{-7}$ )  
733 consistent with these tissues as targets of insulin action (**Figure 5A**). StrEs in individual cell types  
734 showed higher enrichment than super enhancers merged across cell types, highlighting the  
735 importance of cell-specific analyses (**Figure 5A**). HbA1c signals were enriched in StrEs of multiple cell  
736 types and tissues, but have the strongest enrichment in K562 blood-derived leukemia cells (fold-  
737 enrichment=3.24,  $P=1.2 \times 10^{-7}$ , **Figure 5A**). Among the “hard” glycemic and red blood cell (mature +  
738 reticulocyte) HbA1c signals, glycemic signals were enriched in islet StrEs (fold-enrichment=3.96,  
739  $P=3.7 \times 10^{-16}$ ) while red blood cell signals were enriched in K562 StrEs (fold-enrichment=7.5,  
740  $P=2.08 \times 10^{-14}$ , **Figure 5B, Supplementary Table 17**). These analyses suggest that these glycemic trait-  
741 associated variants influence the function of tissue-specific enhancers.

742  
743 Independent analyses with fGWAS<sup>58</sup> and GARFIELD<sup>59</sup> yielded consistent results (**Extended Data**  
744 **Figures 8 and 9, Supplementary Tables 16 and 18**). Notably, FI signals at a lenient threshold of  $P < 10^{-5}$   
745 were enriched in liver StrEs using GARFIELD (odds ratio=1.92,  $P=1.7 \times 10^{-4}$ ) (**Extended Data Figure**  
746 **9A**). This suggests that liver regulatory annotations are relevant for FI GWAS signals, but that we lack  
747 power to detect significant enrichment using the genome-wide significant loci and the current set of  
748 reference annotations.

749  
750 We next explored the 27 loci driving the FI enrichment in adipose and skeletal muscle, 11 of which  
751 overlapped StrEs in both tissues (**Figure 5C**). At the *COL4A2* locus, variants within an intronic region  
752 overlap StrEs in adipose tissue, skeletal muscle, and a human skeletal muscle myoblast (HSMM) cell  
753 line that are not shared across other cell/tissue types. Among these, rs9555695 (in the 99% CS) also  
754 overlaps accessible chromatin regions in adipose (**Figure 5D**). At a narrow signal with no proxy  
755 variants (LD  $r^2 > 0.7$  in Europeans), the lead trans-ancestry variant rs62271373 (PPA = 0.94) located in  
756 an intergenic region  $\sim 25\text{kb}$  from the *LINC01214* gene overlaps StrEs specific to adipose and HSMM  
757 and an active enhancer chromatin state in skeletal muscle (**Figure 5E**). Collectively, the tissue-  
758 specific epigenomic signatures at GWAS signals provide an opportunity to nominate tissues where  
759 these variants are likely to be active. This map may help future efforts to deconvolute GWAS signals  
760 into tissue-specific disease pathology.

#### 761 762 **Co-localization of GWAS and eQTLs**

763 Among the 99 novel glycemic trait loci, we identified co-localized eQTLs at 34 loci in blood,  
764 pancreatic islets, subcutaneous or visceral adipose, skeletal muscle, or liver, providing suggestive  
765 evidence of causal genes (**Supplementary Table 19**). The co-localized eQTLs include several genes  
766 previously reported at glycemic trait loci: *ADCY5*, *CAMK1D*, *IRS1*, *JAZF1*, and *KLF14*<sup>60-62</sup>. For some  
767 additional loci, the co-localized genes have prior evidence for a role in glycemic regulation. For  
768 example, the lead trans-ancestry variant and likely causal variant, rs1799815 (PPA=0.993),  
769 associated with FI is the strongest variant associated with expression of *INSR*, encoding the insulin  
770 receptor, in subcutaneous adipose from METSIM ( $P=2 \times 10^{-9}$ ) and GTEx ( $P=5 \times 10^{-6}$ ). The A allele at  
771 rs1799815 is associated with higher FI and lower expression of *INSR*, consistent with the relationship  
772 between insulin resistance and reduced *INSR* function<sup>63</sup>. In a second example, rs841572, the trans-  
773 ancestry lead variant associated with FG, has the highest PPA (PPA=0.535) among the 20 variants in  
774 the 99% CS and is in strong LD ( $r^2=0.87$ ) with the lead eQTL variant (rs841576, also in the 99% CS)  
775 associated with *SLC2A1* expression in blood (eQTLGen  $P=1 \times 10^{-8}$ ). *SLC2A1*, also known as *GLUT1*,

776 encodes the major glucose transporter in brain, placenta, and erythrocytes, and is responsible for  
777 glucose entry into the brain<sup>64</sup>. rs841572-A is associated with lower FG and lower *SLC2A1* expression.  
778 While rare missense variants in *SLC2A1* are an established cause of seizures and epilepsy<sup>65</sup>, our data  
779 suggest that *SLC2A1* variants also affect plasma glucose levels within a population. These co-  
780 localized signals provide possible regulatory mechanisms for variant effects on genes to influence  
781 glycemic traits.

782  
783 The co-localized eQTLs also provide new insights into the mechanisms at glycemic trait loci. For  
784 example, rs9884482 (in the 99% CS) is associated with FI and *TET2* expression in subcutaneous  
785 adipose ( $P=2\times 10^{-20}$ ); rs9884482 is in high LD ( $r^2=0.96$  in Europeans) with the lead *TET2* eQTL variant  
786 (rs974801). *TET2* encodes a DNA-demethylase that can affect transcriptional repression<sup>66</sup>. Adipose  
787 *Tet2* expression is reduced in diet-induced insulin resistance in mice<sup>67</sup>, and knockdown of *Tet2*  
788 blocked adipogenesis<sup>67,68</sup>. Consistently, in human adipose tissue, rs9884482-C was associated with  
789 lower *TET2* expression and higher FI. In a second example, rs617948 is associated with HbA1c (in the  
790 99% CS) and is the lead variant associated with *C2CD2L* expression in blood (eQTLGen  $P=3\times 10^{-96}$ ).  
791 *C2CD2L*, also known as *TMEM24*, regulates pulsatile insulin secretion and facilitates release of  
792 insulin pool reserves<sup>69,70</sup>. rs617948-G was associated with higher HbA1c and lower *C2CD2L*, providing  
793 evidence for a role of this insulin secretion protein in glucose homeostasis. Our HbA1c “soft”  
794 clustering assigned this signal to both the “unknown” (0.51 probability) and “reticulocyte” (0.42  
795 probability) clusters. rs617948 is strongly associated with HbA1c ( $P<6.8\times 10^{-8}$ ), but not with FG, FI or  
796 2hGlu ( $P>0.05$ , **Supplementary Table 20, Supplementary Note**). This suggests an effect of this  
797 variant on reticulocyte biology, and on insulin secretion, potentially influencing HbA1c levels through  
798 different tissues, and providing a plausible explanation for the classification as “unknown”.

799

#### 800 **Tissue Expression**

801 Consistent with effector transcript expression analysis using GTEx data<sup>30</sup>, we found significant  
802 differences in tissue expression across the glycemic trait signals. FG signals were enriched for genes  
803 expressed in the pancreas (FDR<0.05), while there were an insufficient number of significant  
804 associations in 2hGlu to identify enrichment for any tissue or cell type at FDR<0.2 threshold. FI  
805 signals were enriched for connective tissue and cells (which includes adipose tissue), endocrine  
806 glands, blood cells, and muscles (FDR<0.2) and HbA1c signals were significantly enriched for genes  
807 expressed in the pancreas, hemic, and immune system (FDR<0.05) (**Figure 6, Supplementary Table**  
808 **21**). Consistent with previous analysis<sup>30</sup>, FI-enrichment for connective tissue was driven by adipose  
809 tissue (subcutaneous and visceral), while the newly described enrichment with endocrine glands was  
810 driven by the adrenal glands and cortex (**Supplementary Table 21**). Beyond enrichment for genes  
811 expressed in glycemic-related tissues, HbA1c signals were enriched with genes expressed in blood,  
812 consistent with the role of RBC in this trait and our previous results<sup>30</sup>.

813

814 The association between FI signals and genes expressed in adrenal glands is notable, suggesting a  
815 possible direct role for these genes in insulin resistance. These genes might influence cortisol levels,  
816 which could contribute to insulin resistance and FI levels through impaired insulin receptor signaling  
817 in peripheral tissues, as well as influencing body fat distribution, stimulate lipolysis, and other  
818 indirect mechanisms<sup>71,72</sup>.

819

820

#### 821 **Gene-set Analyses**

822 Next, we performed gene-set analysis using DEPICT (**Methods**). In keeping with previous results<sup>30</sup>,  
823 we found distinct gene-sets enriched (FDR<0.05) for each glycemic trait except 2hGlu, which had  
824 insufficient associations to have power in this analysis. FG-associated variants highlighted gene-sets  
825 involved in metabolism and gene-sets involved in general cellular function such as “cytoplasmic  
826 vesicle membrane” and “circadian clock” (**Figure 7A**). In contrast, in addition to metabolism-related

827 gene-sets, FI-associated variants highlighted pathways related to growth, cancer and reproduction  
828 (**Figure 7B**). This is consistent with the role of insulin as a mitogenic hormone, and with  
829 epidemiological links between insulin and certain types of cancer<sup>73</sup> and reproductive disorders such  
830 as polycystic ovary syndrome<sup>74</sup>. HbA1c-associated variants highlighted many gene-sets (**Figure 7C**),  
831 including those linked to metabolism and hematopoiesis, again recapitulating our postulated effects  
832 of variants on glucose and RBC biology. Additional pathways from HbA1c-associated variants also  
833 highlighted previous “CREBP PPI” and lipid biology related to T2D<sup>75</sup> and HbA1c<sup>76</sup>, respectively, and  
834 potential new biology through which variants may influence HbA1c.

835

## 836 Discussion

837 Here we describe a large glycemic trait meta-analysis of GWAS for which 30% of the population was  
838 composed of East Asian, Hispanic, African-American, South Asian and sub-Saharan African  
839 participants. This effort identified 242 loci (235 trans-ancestry and seven single-ancestry), which  
840 jointly explain between 0.7% (2hGlu in European ancestry individuals) and 6% (HbA1c in African  
841 American ancestry individuals) of the variance in glycemic traits in any given ancestry. While  
842 114/242 loci are associated with T2D ( $P < 10^{-4}$ ; 83 loci with  $P < 5 \times 10^{-8}$ , **Supplementary Table 4**),  
843 absence of strong evidence of association at the remaining loci ( $P \geq 10^{-4}$ ) suggests that for alleles  
844 more frequent than 5% we can exclude T2D ORs  $\geq 1.07$  with 80% power ( $\alpha = 5 \times 10^{-8}$ ; and ORs  $\geq 1.05$   
845 for  $\alpha = 10^{-4}$ ) given a current study of 228,499 T2D cases and 1,178,783 controls<sup>27</sup>. We identified  
846 486 signals associated with glycemic traits, of which eight have MAF  $< 1\%$ , and 45 have  $1\% \leq \text{MAF} < 5\%$   
847 in all ancestries, highlighting that 89% of signals identified are common in at least one ancestry  
848 studied.

849

850 A key aim of our study was to evaluate the added advantage of including population diversity in  
851 genetic discovery and fine-mapping efforts. Beyond the larger sample size included in the trans-  
852 ancestry meta-analysis, we were able to estimate the contribution of non-European ancestry data in  
853 locus discovery and fine-mapping resolution. We found that 24 of the 99 newly discovered loci owe  
854 their discovery to the inclusion of East Asian, Hispanic, African-American, South Asian and sub-  
855 Saharan African participant data, due to differences in EAF and effect sizes across ancestries.

856

857 Comparison of 295 trans-ancestry lead variants (315 locus-trait associations) across ancestries  
858 demonstrated that between 81.5% (HbA1c) and 85.7% (FG) of the trans-ancestry lead variants had  
859 no evidence of trans-ancestry heterogeneity in allelic effects ( $P > 0.05$ ).

860

861 Given sample size and power limitations, genome-wide significant trait-associated variants in a  
862 single-ancestry explain only a modest proportion of trait variance in that ancestry (**Figure 2**). We  
863 demonstrate that trans-ancestry lead variants explain more trait variance than the ancestry-specific  
864 variants (**Figure 2**). This shows that even though some trans-ancestry lead variants are not genome-  
865 wide significant in all ancestries, they contribute to the genetic architecture of the trait in most  
866 ancestries.

867

868 We evaluated for the first time the transferability of European ancestry-derived glycemic trait PGS  
869 into other ancestries. Consistent with other traits<sup>36,77,78</sup>, we confirm that European ancestry-derived  
870 PGS perform much worse when the test dataset is from a different ancestry. Each trait-specific PGS  
871 improves trait variance explained by between 3.5-fold (HbA1c) and 6-fold (FG) in the European  
872 dataset (**Figure 3, Supplementary Table 12**) compared to a score built only from trans-ancestry lead  
873 variants and European index variants (**Figure 2, Supplementary tables 9-12**).

874

875 Despite development of approaches to derive polygenic risk scores<sup>79</sup>, we note the difficulty in using  
876 summary level data to build a PGS in one ancestry and then apply it in test datasets of different  
877 ancestry. While PRS-CSauto<sup>34</sup> is able to use summary level data, revision of the effect size estimates

878 to account for LD required reference panels that matched the ancestry of the test dataset. However,  
879 the current software lacks appropriate reference panels for many ancestries, precluding its broad  
880 application. **Future developments of trans-ancestry PGS are required for improved cross-ancestry**  
881 **performance.**

882

883 We show that fine-mapping resolution is improved in trans-ancestry, compared to single-ancestry  
884 fine-mapping efforts. In ~50% of our loci, we showed that the improvement was due to differences  
885 in EAF, effect size, or LD structure between ancestries, and not just due to the overall increased  
886 sample size available for trans-ancestry fine-mapping. By performing trans-ancestry fine-mapping,  
887 and co-localizing GWAS signals with eQTL signals and coding variants, we identified new candidate  
888 causal genes. Altogether, these results motivate continued expansion of genetic and genomic efforts  
889 in diverse populations to improve understanding of these traits in groups disproportionately affected  
890 by T2D.

891

892 Given data on four different glyceic traits and their utility to diagnose and monitor T2D and  
893 metabolic health, we also sought to characterize biological features underlying these traits. We  
894 show that despite significant sharing of loci across the four traits, each trait is also characterized by  
895 unique features based on StrE, gene expression and gene-set signatures. Combining genetic data  
896 from these traits with T2D data will further elucidate pathways driving normal physiology and  
897 pathophysiology, and help further develop useful predictive scores for disease classification and  
898 management<sup>4,5</sup>.

899

900

## 901 **References**

902

903 1 in *Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus:*  
904 *Abbreviated Report of a WHO Consultation* (World Health Organization

905 Copyright © World Health Organization 2011., 2011).

906 2 Goodarzi, M. O. *et al.* Fasting insulin reflects heterogeneous physiological processes:  
907 role of insulin clearance. *American journal of physiology. Endocrinology and*  
908 *metabolism* **301**, E402-408, doi:10.1152/ajpendo.00013.2011 (2011).

909 3 Dimas, A. S. *et al.* Impact of type 2 diabetes susceptibility variants on quantitative  
910 glyceic traits reveals mechanistic heterogeneity. *Diabetes* **63**, 2158-2171,  
911 doi:10.2337/db13-0949 (2014).

912 4 Udler, M. S. *et al.* Type 2 diabetes genetic loci informed by multi-trait associations  
913 point to disease mechanisms and subtypes: A soft clustering analysis. *PLoS medicine*  
914 **15**, e1002654, doi:10.1371/journal.pmed.1002654 (2018).

915 5 Udler, M. S., McCarthy, M. I., Florez, J. C. & Mahajan, A. Genetic Risk Scores for  
916 Diabetes Diagnosis and Precision Medicine. *Endocrine reviews* **40**, 1500-1520,  
917 doi:10.1210/er.2019-00088 (2019).

918 6 Sarwar, N. *et al.* Diabetes mellitus, fasting blood glucose concentration, and risk of  
919 vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet*  
920 **375**, 2215-2222, doi:10.1016/s0140-6736(10)60484-9 (2010).

921 7 Wheeler, E. *et al.* Impact of common genetic determinants of Hemoglobin A1c on  
922 type 2 diabetes risk and diagnosis in ancestrally diverse populations: A transethnic  
923 genome-wide meta-analysis. *PLoS medicine* **14**, e1002383,  
924 doi:10.1371/journal.pmed.1002383 (2017).

925 8 Dupuis, J. *et al.* New genetic loci implicated in fasting glucose homeostasis and their  
926 impact on type 2 diabetes risk. *Nature genetics* **42**, 105-116, doi:10.1038/ng.520  
927 (2010).

928 9 Manning, A. K. *et al.* A genome-wide approach accounting for body mass index  
929 identifies genetic variants influencing fasting glycaemic traits and insulin resistance.  
930 *Nature genetics* **44**, 659-669, doi:10.1038/ng.2274 (2012).

931 10 Walford, G. A. *et al.* Genome-Wide Association Study of the Modified Stumvoll  
932 Insulin Sensitivity Index Identifies BCL2 and FAM19A2 as Novel Insulin Sensitivity  
933 Loci. *Diabetes* **65**, 3200-3211, doi:10.2337/db16-0199 (2016).

934 11 Horikoshi, M. *et al.* Discovery and Fine-Mapping of Glycaemic and Obesity-Related  
935 Trait Loci Using High-Density Imputation. *PLoS genetics* **11**, e1005230,  
936 doi:10.1371/journal.pgen.1005230 (2015).

937 12 Mahajan, A. *et al.* Identification and functional characterization of G6PC2 coding  
938 variants influencing glycaemic traits define an effector transcript at the G6PC2-  
939 ABCB11 locus. *PLoS genetics* **11**, e1004876, doi:10.1371/journal.pgen.1004876  
940 (2015).

941 13 Hwang, J. Y. *et al.* Genome-wide association meta-analysis identifies novel variants  
942 associated with fasting plasma glucose in East Asians. *Diabetes* **64**, 291-298,  
943 doi:10.2337/db14-0563 (2015).

944 14 Chen, P. *et al.* Multiple nonglycaemic genomic loci are newly associated with blood  
945 level of glycaated hemoglobin in East Asians. *Diabetes* **63**, 2551-2562,  
946 doi:10.2337/db13-1815 (2014).

947 15 Scott, R. A. *et al.* Large-scale association analyses identify new loci influencing  
948 glycaemic traits and provide insight into the underlying biological pathways. *Nature*  
949 *genetics* **44**, 991-1005, doi:10.1038/ng.2385 (2012).

950 16 Spanakis, E. K. & Golden, S. H. Race/ethnic difference in diabetes and diabetic  
951 complications. *Current diabetes reports* **13**, 814-823, doi:10.1007/s11892-013-0421-  
952 9 (2013).

953 17 Tillin, T. *et al.* Insulin resistance and truncal obesity as important determinants of the  
954 greater incidence of diabetes in Indian Asians and African Caribbeans compared with  
955 Europeans: the Southall And Brent REvisited (SABRE) cohort. *Diabetes care* **36**, 383-  
956 393, doi:10.2337/dc12-0544 (2013).

957 18 Whincup, P. H. *et al.* Early emergence of ethnic differences in type 2 diabetes  
958 precursors in the UK: the Child Heart and Health Study in England (CHASE Study).  
959 *PLoS medicine* **7**, e1000263, doi:10.1371/journal.pmed.1000263 (2010).

960 19 Auton, A. *et al.* A global reference for human genetic variation. *Nature* **526**, 68-74,  
961 doi:10.1038/nature15393 (2015).

962 20 Willer, C. J., Li, Y. & Abecasis, G. R. METAL: fast and efficient meta-analysis of  
963 genomewide association scans. *Bioinformatics (Oxford, England)* **26**, 2190-2191,  
964 doi:10.1093/bioinformatics/btq340 (2010).

965 21 Yang, J., Lee, S. H., Goddard, M. E. & Visscher, P. M. GCTA: a tool for genome-wide  
966 complex trait analysis. *American journal of human genetics* **88**, 76-82,  
967 doi:10.1016/j.ajhg.2010.11.011 (2011).

968 22 Yang, J. *et al.* Conditional and joint multiple-SNP analysis of GWAS summary statistics  
969 identifies additional variants influencing complex traits. *Nature genetics* **44**, 369-375,  
970 s361-363, doi:10.1038/ng.2213 (2012).

971 23 Genome-wide association study of 14,000 cases of seven common diseases and  
972 3,000 shared controls. *Nature* **447**, 661-678, doi:10.1038/nature05911 (2007).

973 24 Mahajan, A. *et al.* Trans-ancestry genetic study of type 2 diabetes highlights the  
974 power of diverse populations for discovery and translation. *medRxiv*,  
975 2020.2009.2022.20198937, doi:10.1101/2020.09.22.20198937 (2020).

976 25 Mahajan, A. *et al.* Fine-mapping type 2 diabetes loci to single-variant resolution  
977 using high-density imputation and islet-specific epigenome maps. *Nature genetics*  
978 **50**, 1505-1513, doi:10.1038/s41588-018-0241-6 (2018).

979 26 Spracklen, C. N. *et al.* Identification of type 2 diabetes loci in 433,540 East Asian  
980 individuals. *Nature* **582**, 240-245, doi:10.1038/s41586-020-2263-3 (2020).

981 27 Vujkovic, M. *et al.* Discovery of 318 new risk loci for type 2 diabetes and related  
982 vascular outcomes among 1.4 million participants in a multi-ancestry meta-analysis.  
983 *Nature genetics* **52**, 680-691, doi:10.1038/s41588-020-0637-y (2020).

984 28 Luo, Y. *et al.* Transcription factor Ets1 regulates expression of thioredoxin-interacting  
985 protein and inhibits insulin secretion in pancreatic beta-cells. *PLoS one* **9**, e99049,  
986 doi:10.1371/journal.pone.0099049 (2014).

987 29 Braccini, L. *et al.* PI3K-C2gamma is a Rab5 effector selectively controlling endosomal  
988 Akt2 activation downstream of insulin signalling. *Nature communications* **6**, 7400,  
989 doi:10.1038/ncomms8400 (2015).

990 30 Ng, N. H. J. *et al.* Tissue-Specific Alteration of Metabolic Pathways Influences  
991 Glycemic Regulation. *bioRxiv*, 790618, doi:10.1101/790618 (2019).

992 31 Aschard, H., Vilhjalmsson, B. J., Joshi, A. D., Price, A. L. & Kraft, P. Adjusting for  
993 heritable covariates can bias effect estimates in genome-wide association studies.  
994 *American journal of human genetics* **96**, 329-339, doi:10.1016/j.ajhg.2014.12.021  
995 (2015).

996 32 Lee, J. J. *et al.* Gene discovery and polygenic prediction from a genome-wide  
997 association study of educational attainment in 1.1 million individuals. *Nature*  
998 *genetics* **50**, 1112-1121, doi:10.1038/s41588-018-0147-3 (2018).

999 33 Nolte, I. M. *et al.* Missing heritability: is the gap closing? An analysis of 32 complex  
1000 traits in the Lifelines Cohort Study. *European journal of human genetics : EJHG* **25**,  
1001 877-885, doi:10.1038/ejhg.2017.50 (2017).

1002 34 Ge, T., Chen, C. Y., Ni, Y., Feng, Y. A. & Smoller, J. W. Polygenic prediction via  
1003 Bayesian regression and continuous shrinkage priors. *Nature communications* **10**,  
1004 1776, doi:10.1038/s41467-019-09718-5 (2019).

1005 35 Dastani, Z. *et al.* Novel loci for adiponectin levels and their influence on type 2  
1006 diabetes and metabolic traits: a multi-ethnic meta-analysis of 45,891 individuals.  
1007 *PLoS genetics* **8**, e1002607, doi:10.1371/journal.pgen.1002607 (2012).

1008 36 Martin, A. R. *et al.* Clinical use of current polygenic risk scores may exacerbate health  
1009 disparities. *Nature genetics* **51**, 584-591, doi:10.1038/s41588-019-0379-x (2019).

1010 37 Gaulton, K. J. *et al.* Genetic fine mapping and genomic annotation defines causal  
1011 mechanisms at type 2 diabetes susceptibility loci. *Nature genetics* **47**, 1415-1425,  
1012 doi:10.1038/ng.3437 (2015).

1013 38 Spracklen, C. N. *et al.* Identification and functional analysis of glycemic trait loci in  
1014 the China Health and Nutrition Survey. *PLoS genetics* **14**, e1007275,  
1015 doi:10.1371/journal.pgen.1007275 (2018).

1016 39 Varshney, A. *et al.* Genetic regulatory signatures underlying islet gene expression  
1017 and type 2 diabetes. *Proceedings of the National Academy of Sciences of the United*  
1018 *States of America* **114**, 2301-2306, doi:10.1073/pnas.1621192114 (2017).

1019 40 Kichaev, G. *et al.* Leveraging Polygenic Functional Enrichment to Improve GWAS  
1020 Power. *American journal of human genetics* **104**, 65-75,  
1021 doi:10.1016/j.ajhg.2018.11.008 (2019).

1022 41 Shriner, D. & Rotimi, C. N. Whole-Genome-Sequence-Based Haplotypes Reveal Single  
1023 Origin of the Sickle Allele during the Holocene Wet Phase. *American journal of*  
1024 *human genetics* **102**, 547-556, doi:10.1016/j.ajhg.2018.02.003 (2018).

1025 42 Kramer, H. J. *et al.* African Ancestry-Specific Alleles and Kidney Disease Risk in  
1026 Hispanics/Latinos. *Journal of the American Society of Nephrology : JASN* **28**, 915-922,  
1027 doi:10.1681/asn.2016030357 (2017).

1028 43 Ravenhall, M. *et al.* Novel genetic polymorphisms associated with severe malaria and  
1029 under selective pressure in North-eastern Tanzania. *PLoS genetics* **14**, e1007172,  
1030 doi:10.1371/journal.pgen.1007172 (2018).

1031 44 Hodonsky, C. J. *et al.* Genome-wide association study of red blood cell traits in  
1032 Hispanics/Latinos: The Hispanic Community Health Study/Study of Latinos. *PLoS*  
1033 *genetics* **13**, e1006760, doi:10.1371/journal.pgen.1006760 (2017).

1034 45 Gurdasani, D. *et al.* Uganda Genome Resource Enables Insights into Population  
1035 History and Genomic Discovery in Africa. *Cell* **179**, 984-1002.e1036,  
1036 doi:10.1016/j.cell.2019.10.004 (2019).

1037 46 Rees, M. G. *et al.* Cellular characterisation of the GCKR P446L variant associated with  
1038 type 2 diabetes risk. *Diabetologia* **55**, 114-122, doi:10.1007/s00125-011-2348-5  
1039 (2012).

1040 47 Bonomo, J. A. *et al.* The ras responsive transcription factor RREB1 is a novel  
1041 candidate gene for type 2 diabetes associated end-stage kidney disease. *Human*  
1042 *molecular genetics* **23**, 6441-6447, doi:10.1093/hmg/ddu362 (2014).

1043 48 Wessel, J. *et al.* Low-frequency and rare exome chip variants associate with fasting  
1044 glucose and type 2 diabetes susceptibility. *Nature communications* **6**, 5897,  
1045 doi:10.1038/ncomms6897 (2015).

1046 49 Scott, R. A. *et al.* A genomic approach to therapeutic target validation identifies a  
1047 glucose-lowering GLP1R variant protective for coronary heart disease. *Science*  
1048 *translational medicine* **8**, 341ra376, doi:10.1126/scitranslmed.aad3744 (2016).

1049 50 Nai, A. *et al.* TMPRSS6 rs855791 modulates hepcidin transcription in vitro and serum  
1050 hepcidin levels in normal individuals. *Blood* **118**, 4459-4462, doi:10.1182/blood-  
1051 2011-06-364034 (2011).

1052 51 Soranzo, N. *et al.* Common variants at 10 genomic loci influence hemoglobin A(1)(C)  
1053 levels via glycemc and nonglycemc pathways. *Diabetes* **59**, 3229-3239,  
1054 doi:10.2337/db10-0502 (2010).

1055 52 Sarnowski, C. *et al.* Impact of Rare and Common Genetic Variants on Diabetes  
1056 Diagnosis by Hemoglobin A1c in Multi-Ancestry Cohorts: The Trans-Omics for  
1057 Precision Medicine Program. *American journal of human genetics* **105**, 706-718,  
1058 doi:10.1016/j.ajhg.2019.08.010 (2019).

1059 53 Kundaje, A. *et al.* Integrative analysis of 111 reference human epigenomes. *Nature*  
1060 **518**, 317-330, doi:10.1038/nature14248 (2015).

1061 54 Nagel, M. *et al.* Meta-analysis of genome-wide association studies for neuroticism in  
1062 449,484 individuals identifies novel genetic loci and pathways. *Nature genetics* **50**,  
1063 920-927, doi:10.1038/s41588-018-0151-7 (2018).

1064 55 Savage, J. E. *et al.* Genome-wide association meta-analysis in 269,867 individuals  
1065 identifies new genetic and functional links to intelligence. *Nature genetics* **50**, 912-  
1066 919, doi:10.1038/s41588-018-0152-6 (2018).

1067 56 Schmidt, E. M. *et al.* GREGOR: evaluating global enrichment of trait-associated  
1068 variants in epigenomic features using a systematic, data-driven approach.  
1069 *Bioinformatics (Oxford, England)* **31**, 2601-2606, doi:10.1093/bioinformatics/btv201  
1070 (2015).

1071 57 Parker, S. C. *et al.* Chromatin stretch enhancer states drive cell-specific gene  
1072 regulation and harbor human disease risk variants. *Proceedings of the National  
1073 Academy of Sciences of the United States of America* **110**, 17921-17926,  
1074 doi:10.1073/pnas.1317023110 (2013).

1075 58 Pickrell, J. K. Joint analysis of functional genomic data and genome-wide association  
1076 studies of 18 human traits. *American journal of human genetics* **94**, 559-573,  
1077 doi:10.1016/j.ajhg.2014.03.004 (2014).

1078 59 Iotchkova, V. *et al.* GARFIELD classifies disease-relevant genomic features through  
1079 integration of functional annotations with association signals. *Nature genetics* **51**,  
1080 343-353, doi:10.1038/s41588-018-0322-6 (2019).

1081 60 van de Bunt, M. *et al.* Transcript Expression Data from Human Islets Links Regulatory  
1082 Signals from Genome-Wide Association Studies for Type 2 Diabetes and Glycemic  
1083 Traits to Their Downstream Effectors. *PLoS genetics* **11**, e1005694,  
1084 doi:10.1371/journal.pgen.1005694 (2015).

1085 61 Civelek, M. *et al.* Genetic Regulation of Adipose Gene Expression and Cardio-  
1086 Metabolic Traits. *American journal of human genetics* **100**, 428-443,  
1087 doi:10.1016/j.ajhg.2017.01.027 (2017).

1088 62 Scott, L. J. *et al.* The genetic regulatory signature of type 2 diabetes in human  
1089 skeletal muscle. *Nature communications* **7**, 11764, doi:10.1038/ncomms11764  
1090 (2016).

1091 63 Ben Harouch, S., Klar, A. & Falik Zaccai, T. C. in *GeneReviews((R))* (eds M. P. Adam *et*  
1092 *al.*) (University of Washington, Seattle  
1093 University of Washington, Seattle. GeneReviews is a registered trademark of the University  
1094 of Washington, Seattle. All rights reserved., 1993).

1095 64 Agus, D. B. *et al.* Vitamin C crosses the blood-brain barrier in the oxidized form  
1096 through the glucose transporters. *The Journal of clinical investigation* **100**, 2842-  
1097 2848, doi:10.1172/jci119832 (1997).

1098 65 Wolking, S. *et al.* Focal epilepsy in glucose transporter type 1 (Glut1) defects: case  
1099 reports and a review of literature. *Journal of neurology* **261**, 1881-1886,  
1100 doi:10.1007/s00415-014-7433-5 (2014).

1101 66 Guallar, D. *et al.* RNA-dependent chromatin targeting of TET2 for endogenous  
1102 retrovirus control in pluripotent stem cells. *Nature genetics* **50**, 443-451,  
1103 doi:10.1038/s41588-018-0060-9 (2018).

1104 67 Bian, F. *et al.* TET2 facilitates PPARgamma agonist-mediated gene regulation and  
1105 insulin sensitization in adipocytes. *Metabolism: clinical and experimental* **89**, 39-47,  
1106 doi:10.1016/j.metabol.2018.08.006 (2018).



1107 68 Yoo, Y. *et al.* TET-mediated hydroxymethylcytosine at the Ppargamma locus is  
1108 required for initiation of adipogenic differentiation. *International journal of obesity*  
1109 (2005) **41**, 652-659, doi:10.1038/ijo.2017.8 (2017).

1110 69 Lees, J. A. *et al.* Lipid transport by TMEM24 at ER-plasma membrane contacts  
1111 regulates pulsatile insulin secretion. *Science (New York, N.Y.)* **355**,  
1112 doi:10.1126/science.aah6171 (2017).

1113 70 Pottekat, A. *et al.* Insulin biosynthetic interaction network component, TMEM24,  
1114 facilitates insulin reserve pool release. *Cell reports* **4**, 921-930,  
1115 doi:10.1016/j.celrep.2013.07.050 (2013).

1116 71 Androulakis, I *et al.* Patients with apparently nonfunctioning adrenal incidentalomas  
1117 may be at increased cardiovascular risk due to excessive cortisol secretion. *The*  
1118 *Journal of clinical endocrinology and metabolism* **99**, 2754-2762,  
1119 doi:10.1210/jc.2013-4064 (2014).

1120 72 Altieri, B. *et al.* Adrenocortical tumors and insulin resistance: What is the first step?  
1121 *International journal of cancer* **138**, 2785-2794, doi:10.1002/ijc.29950 (2016).

1122 73 Johansson, M. *et al.* The influence of obesity-related factors in the etiology of renal  
1123 cell carcinoma-A mendelian randomization study. *PLoS medicine* **16**, e1002724,  
1124 doi:10.1371/journal.pmed.1002724 (2019).

1125 74 Diamanti-Kandarakis, E. & Dunaif, A. Insulin resistance and the polycystic ovary  
1126 syndrome revisited: an update on mechanisms and implications. *Endocrine reviews*  
1127 **33**, 981-1030, doi:10.1210/er.2011-1034 (2012).

1128 75 Morris, A. P. *et al.* Large-scale association analysis provides insights into the genetic  
1129 architecture and pathophysiology of type 2 diabetes. *Nature genetics* **44**, 981-990,  
1130 doi:10.1038/ng.2383 (2012).

1131 76 Leong, A. *et al.* Mendelian Randomization Analysis of Hemoglobin A(1c) as a Risk  
1132 Factor for Coronary Artery Disease. *Diabetes care* **42**, 1202-1208, doi:10.2337/dc18-  
1133 1712 (2019).

1134 77 Duncan, L. *et al.* Analysis of polygenic risk score usage and performance in diverse  
1135 human populations. *Nature communications* **10**, 3328, doi:10.1038/s41467-019-  
1136 11112-0 (2019).

1137 78 Mostafavi, H. *et al.* Variable prediction accuracy of polygenic scores within an  
1138 ancestry group. *eLife* **9**, doi:10.7554/eLife.48376 (2020).

1139 79 Choi, S. W., Mak, T. S. & O'Reilly, P. F. Tutorial: a guide to performing polygenic risk  
1140 score analyses. *Nature protocols* **15**, 2759-2772, doi:10.1038/s41596-020-0353-1  
1141 (2020).

1142 80 D'Orazio, P. *et al.* Approved IFCC recommendation on reporting results for blood  
1143 glucose (abbreviated). *Clinical chemistry* **51**, 1573-1576,  
1144 doi:10.1373/clinchem.2005.051979 (2005).

1145 81 Voight, B. F. *et al.* The metabochip, a custom genotyping array for genetic studies of  
1146 metabolic, cardiovascular, and anthropometric traits. *PLoS genetics* **8**, e1002793,  
1147 doi:10.1371/journal.pgen.1002793 (2012).

1148 82 Abecasis, G. R. *et al.* An integrated map of genetic variation from 1,092 human  
1149 genomes. *Nature* **491**, 56-65, doi:10.1038/nature11632 (2012).

1150 83 Li, Y., Willer, C. J., Ding, J., Scheet, P. & Abecasis, G. R. MaCH: using sequence and  
1151 genotype data to estimate haplotypes and unobserved genotypes. *Genetic*  
1152 *epidemiology* **34**, 816-834, doi:10.1002/gepi.20533 (2010).

1153 84 Pei, Y. F., Zhang, L., Li, J. & Deng, H. W. Analyses and comparison of imputation-  
1154 based association methods. *PLoS one* **5**, e10827, doi:10.1371/journal.pone.0010827  
1155 (2010).

1156 85 Winkler, T. W. *et al.* Quality control and conduct of genome-wide association meta-  
1157 analyses. *Nature protocols* **9**, 1192-1212, doi:10.1038/nprot.2014.071 (2014).

1158 86 Devlin, B. & Roeder, K. Genomic control for association studies. *Biometrics* **55**, 997-  
1159 1004 (1999).

1160 87 Morris, A. P. Transethnic meta-analysis of genomewide association studies. *Genetic  
1161 epidemiology* **35**, 809-822, doi:10.1002/gepi.20630 (2011).

1162 88 Bulik-Sullivan, B. K. *et al.* LD Score regression distinguishes confounding from  
1163 polygenicity in genome-wide association studies. *Nature genetics* **47**, 291-295,  
1164 doi:10.1038/ng.3211 (2015).

1165 89 Dastani, Z. *et al.* Novel loci for adiponectin levels and their influence on type 2  
1166 diabetes and metabolic traits: a multi-ethnic meta-analysis of 45,891 individuals.  
1167 *PLoS genetics* **8**, e1002607, doi:10.1371/journal.pgen.1002607 (2012).

1168 90 Benner, C. *et al.* FINEMAP: efficient variable selection using summary data from  
1169 genome-wide association studies. *Bioinformatics (Oxford, England)* **32**, 1493-1501,  
1170 doi:10.1093/bioinformatics/btw018 (2016).

1171 91 Astle, W. J. *et al.* The Allelic Landscape of Human Blood Cell Trait Variation and Links  
1172 to Common Complex Disease. *Cell* **167**, 1415-1429.e1419,  
1173 doi:10.1016/j.cell.2016.10.042 (2016).

1174 92 Canela-Xandri, O., Rawlik, K. & Tenesa, A. An atlas of genetic associations in UK  
1175 Biobank. *Nature genetics* **50**, 1593-1599, doi:10.1038/s41588-018-0248-z (2018).

1176 93 Benyamin, B. *et al.* Novel loci affecting iron homeostasis and their effects in  
1177 individuals at risk for hemochromatosis. *Nature communications* **5**, 4926,  
1178 doi:10.1038/ncomms5926 (2014).

1179 94 Binesh, N. & Rezghi, M. Fuzzy clustering in community detection based on  
1180 nonnegative matrix factorization with two novel evaluation criteria. *Applied Soft  
1181 Computing* **69**, 689-703 (2018).

1182 95 Scott, R. A. *et al.* An Expanded Genome-Wide Association Study of Type 2 Diabetes in  
1183 Europeans. *Diabetes* **66**, 2888-2902, doi:10.2337/db16-1253 (2017).

1184 96 Ernst, J. *et al.* Mapping and analysis of chromatin state dynamics in nine human cell  
1185 types. *Nature* **473**, 43-49, doi:10.1038/nature09906 (2011).

1186 97 Mikkelsen, T. S. *et al.* Comparative epigenomic analysis of murine and human  
1187 adipogenesis. *Cell* **143**, 156-169, doi:10.1016/j.cell.2010.09.006 (2010).

1188 98 Ernst, J. & Kellis, M. ChromHMM: automating chromatin-state discovery and  
1189 characterization. *Nature methods* **9**, 215-216, doi:10.1038/nmeth.1906 (2012).

1190 99 Battle, A., Brown, C. D., Engelhardt, B. E. & Montgomery, S. B. Genetic effects on  
1191 gene expression across human tissues. *Nature* **550**, 204-213,  
1192 doi:10.1038/nature24277 (2017).

1193 100 Zhernakova, D. V. *et al.* Identification of context-dependent expression quantitative  
1194 trait loci in whole blood. *Nature genetics* **49**, 139-145, doi:10.1038/ng.3737 (2017).

1195 101 Westra, H. J. *et al.* Systematic identification of trans eQTLs as putative drivers of  
1196 known disease associations. *Nature genetics* **45**, 1238-1243, doi:10.1038/ng.2756  
1197 (2013).

- 1198 102 Joehanes, R. *et al.* Integrated genome-wide analysis of expression quantitative trait  
 1199 loci aids interpretation of genomic association studies. *Genome biology* **18**, 16,  
 1200 doi:10.1186/s13059-016-1142-6 (2017).  
 1201 103 Pers, T. H. *et al.* Biological interpretation of genome-wide association studies using  
 1202 predicted gene functions. *Nature communications* **6**, 5890,  
 1203 doi:10.1038/ncomms6890 (2015).  
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## 1246 Competing interests statement

1248 A. Astrup is the recipient of honoraria as speaker for a wide range of Danish and international  
1249 concerns and receives royalties from textbooks, and from popular diet and cookery books. A. Astrup  
1250 is also co-inventor of a number of patents, including Methods of inducing weight loss, treating  
1251 obesity and preventing weight gain (licensee Gelesis, USA) and Biomarkers for predicting degree of  
1252 weight loss (licensee Nestec SA, CH), owned by the University of Copenhagen, in accordance with  
1253 Danish law. I. Barroso and spouse own stock in GlaxoSmithKline and Incyte Corporation. B.H. Chen is  
1254 now an employee of Life Epigenetics, Inc.; all work was completed prior to employment at Life  
1255 Epigenetics. A.Y. Chu is now an employee of Merck & Co.; all work was completed prior to  
1256 employment by Merck & Co. J.C. Florez has received consulting honoraria from Janssen. J. Gayan is  
1257 now an employee of F. Hoffmann-La Roche Ltd, and owns stock of Roche and GlaxoSmithKline. A.L.  
1258 Gloyn has received honoraria from Merck and Novo Nordisk. As of June 2019, ALG discloses that her  
1259 spouse is an employee of Genentech and hold stock options in Roche. E. Ingelsson is now an  
1260 employee of GSK; all work was completed prior to his employment by GSK. W. März has received  
1261 grants and/or personal fees from the following companies/corporations: Siemens Healthineers,  
1262 Aegerion Pharmaceuticals, AMGEN, Astrazeneca, Sanofi, Alexion Pharmaceuticals, BASF, Abbott  
1263 Diagnostics Numares AG, Berlin-Chemie, Akzea Therapeutics, Bayer Vital GmbH, bestbion dx GmbH,  
1264 Boehringer Ingelheim Pharma GmbH Co KG, Immundiagnostik GmbH, Merck Chemicals GmbH, MSD  
1265 Sharp and Dohme GmbH, Novartis Pharma GmbH, Olink Proteomics, and Synlab Holding  
1266 Deutschland GmbH. M.I. McCarthy has served on advisory panels for Pfizer, NovoNordisk, Zoe Global  
1267 and received honoraria from Merck, Pfizer, NovoNordisk and Eli Lilly. He holds stock options in Zoe  
1268 Global and has received research funding from Abbvie, Astra Zeneca, Boehringer Ingelheim, Eli Lilly,  
1269 Janssen, Merck, NovoNordisk, Pfizer, Roche, Sanofi Aventis, Servier, Takeda. He is now an employee  
1270 of Genentech and a holder of Roche stock. J.B. Meigs has consulted for Quest Diagnostics, Inc., who  
1271 manufacturers of an HbA1c assay. M.E. Montasser has received grant funding from Regeneron  
1272 Pharmaceutials. M.E. Montasser is also an inventor on a patent that was published by the United  
1273 States Patent and Trademark Office on December 6, 2018 under Publication Number US 2018-  
1274 0346888, and international patent application that was published on December 13, 2018 under  
1275 Publication Number WO-2018/226560; all work was completed before these COI arose, and are  
1276 unrelated to this work. D. Mook-Kanamori is a part-time clinical research consultant for Metabolon.  
1277 J.L. Nadler is a member of the Scientific Advisory Board for Veralox Therapeutics Inc. C.N.A. Palmer  
1278 has received research support from GlaxoSmithKline and AstraZeneca unrelated to this project. B.M.  
1279 Psaty serves on the Steering Committee of the Yale Open Data Access Project funded by Johnson &  
1280 Johnson. N. Sattar has consulted for Astrazeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Napp  
1281 and Sanofi and received grant support from Boehringer Ingelheim. R.A. Scott is an employee and  
1282 shareholder of GlaxoSmithKline. T. Spector is the founder of Zoe Global Ltd. J. Tuomilehto receives  
1283 research support from Bayer, is a consultant for Eli Lily, and holds stock in Orion Pharma and  
1284 Aktivolabs Ltd.

1285

## 1286 **Figure Legends**

1287

1288 **Figure 1 - Summary of all 242 loci identified in this study.** 235 trans-ancestry loci are shown in  
1289 orange (novel) or black (established) along with seven single-ancestry loci (blue) represented by  
1290 nearest gene. Each locus is mapped to corresponding chromosome (outer segment). Each set of  
1291 rows shows the results from the trans-ancestry analysis (orange) and each of the ancestries:  
1292 European (purple), African American (tan), East Asian (grey), South Asian (green), Hispanic (yellow),  
1293 sub-Saharan African (Ugandan-pink). Loci with a corresponding type 2 diabetes signal are  
1294 represented by red circles in the middle of the plot.

1295 **Figure 2 – Trait variance explained by associated loci.** The boxplots show the maximum, first  
1296 quartile, median, third quartile and minimum of trait variance explained when using a genetic score  
1297 with single-ancestry lead and index variants (EUR, AA, EAS, HISP and SAS) or a combination of  
1298 individual trait trans-ancestry lead variants and single-ancestry lead and index variants (TA+EUR,

1299 TA+AA, TA+EAS, TA+HISP and TA+SAS). Variance explained for each trait (FG, FI and HbA1c) in each  
1300 ancestry is shown on different panels and in different colors.  $R^2$  was estimated in 1 to 11 cohorts  
1301 with sample sizes ranging from 489 to 9,758 (**Supplementary Tables 8-11**).

1302 **Figure 3 – Transferability of PGS across ancestries.** For each trait, the barplots represent trait  
1303 variance explained when using a European ancestry-derived PGS in European, East Asian and African  
1304 American test datasets. Variance explained (the height of each bar) for each trait (FG, FI and HbA1c)  
1305 in each ancestry is shown on different panels and in different colors.

1306  
1307 **Figure 4 - Trans-ancestry fine-mapping.** A) Number of plausible causal variants at each locus-trait  
1308 association derived from FINEMAP. B) Number of variants within each 99% credible set. Twenty-one  
1309 locus-trait associations at 19 loci were mapped to a single variant in the 99% credible set. C) Fine-  
1310 mapping resolution. For each of the 98 locus-trait associations with a predicted single causal variant  
1311 in both trans-ancestry and single-ancestry analyses, the number of variants included in the 99%  
1312 credible set in the single-ancestry fine-mapping (x axis; logarithmic scale) is plotted against those in  
1313 the trans-ancestry fine-mapping (y axis; logarithmic scale). Trans-ancestry and single-ancestry fine-  
1314 mapping were based on the same set of variants. After removing eight locus-trait associations with  
1315 one variant in the 99% credible sets in both trans-ancestry and single-ancestry analyses, there were  
1316 18 locus-trait associations (in grey) where trans-ancestry fine-mapping did not improve the  
1317 resolution of fine-mapping results (i.e. number of variants in the 99% credible set did not decrease).  
1318 Of the 72 locus-trait associations with improved trans-ancestry fine-mapping resolution (blue and  
1319 red) further analyses in European fine-mapping emulating the total sample size in trans-ancestry  
1320 fine-mapping demonstrated that 34 locus-trait associations (in red) were improved because of both  
1321 total sample size and differences across ancestries, while 38 locus-trait associations (in blue) were  
1322 only improved due to increased sample size in the original trans-ancestry fine-mapping analysis.

1323 **Figure 5 - Epigenomic landscape of trait-associated variants.** A: Enrichment of GWAS variants to  
1324 overlap genomic regions including ‘Static Annotations’ which are common or ‘static’ across cell types  
1325 and ‘Stretch Enhancers’ which are identified in each tissue/cell type. The numbers of signals for each  
1326 trait are indicated in parentheses. Enrichment was calculated using GREGOR<sup>56</sup>. One-sided test for  
1327 significance (red) is determined after Bonferroni correction to account for 59 total annotations  
1328 tested for each trait; nominal significance ( $P < 0.05$ ) is indicated in yellow. B: Enrichment for HbA1c  
1329 GWAS signals partitioned into “hard” Glycemic and Red Blood Cell cluster (signals from “hard”  
1330 mature Red Blood Cell and reticulocyte clusters together) to overlap annotations including StrEs in  
1331 Islets and the blood-derived leukemia cell line K562, respectively (additional partitioned results in  
1332 **Supplementary Table 17**). C: Individual FI GWAS signals that drive enrichment in Adipose and  
1333 Skeletal Muscle StrEs. D, E: Genome browser shots of FI GWAS signals – intronic region of the  
1334 *COL4A2* gene (D) and an inter-genic region ~25kb from *LINC01214* gene (E) showing GWAS SNPs  
1335 (lead and LD  $r^2 > 0.8$  proxies), ATAC-seq signal tracks and chromatin state annotations in different  
1336 tissues/cell types.

1337 **Figure 6 - Tissues and cell types significantly enriched for genes within glycemic-associated loci.**  
1338 Top panel FG-associated loci, middle panel FI-associated loci, bottom panel HbA1c-associated loci.  
1339 FDR thresholds are shown in red ( $q < 0.05$ ), orange ( $q < 0.2$ ), grey ( $q \geq 0.2$ ).

1340 **Figure 7 - Gene-set enrichment analyses.** Results from affinity-propagation clustering of significantly  
1341 enriched gene-sets ( $FDR < 0.05$ ) identified by DEPICT for A) FG, B) FI, and C) HbA1c. Each node is a  
1342 cluster of gene-sets represented by an exemplar gene-set with similarities between the clusters  
1343 represented by the Pearson correlation coefficients ( $r > 0.3$ ). The nodes are colored according to the  
1344 minimum gene-set enrichment p-value for gene-sets in that cluster. Example clusters are expanded  
1345 to show the contributing gene-sets.

1346

1347 **Tables**

1348

1349 **Table 1 – Glossary of terms** - This study combined analyses of trait-associations across multiple correlated  
 1350 glycemic traits and across multiple ancestries, which has presented challenges in our ability to apply commonly  
 1351 used terms with clarity. For this reason, we define below terms often used in the field with variable meaning,  
 1352 as well as definitions of new terms used in this study.

1353

Term	Definition
EA (Effect allele)	The effect allele was that defined by METAL based on trans-ancestry FG results and aligned such that the same allele was kept as the effect allele across all ancestries and traits, irrespective of its allele frequency or effect size for that particular ancestry and trait, in this way the effect allele is not necessarily the trait-increasing allele.
Single-ancestry lead variant	Variant with the smallest p-value amongst all with $P < 5 \times 10^{-8}$ , within a 1Mb region, based on analysis of a single trait in a single ancestry.
Single-ancestry index variants	Variants identified by GCTA analysis of each autosome, and that appear to exert conditionally distinct effects on a given trait in a given ancestry ( $P < 5 \times 10^{-8}$ ). As defined, these include the single-ancestry lead variants.
Trans-ancestry lead variant	Variant identified by trans-ethnic meta-analysis of a given trait that has the strongest association for that trait ( $\log_{10}BF > 6$ , which is broadly equivalent to $P < 5 \times 10^{-8}$ ) within a 1Mb region.
Single-ancestry locus	1Mb region centred on a single-ancestry lead variant which does not contain a lead variant identified in the trans-ancestry meta-analysis (i.e., does not contain a trans-ancestry lead variant).
Signal	Conditionally independent association between a trait and a set of variants in LD with each other and which is noted by the corresponding index variant.
Trans-ancestry locus	A genomic interval that contains trans-ancestry trait-specific lead variants, with/out additional single-ancestry index variants, for one or more traits. This region is defined by starting at the telomere of each chromosome and selecting the first single-ancestry index variant or trans-ancestry lead variant for any trait. If other trans-ancestry lead variants or single-ancestry index variants mapped within 500kb of the first signal, then they were merged into the same locus. This process was repeated until there were no more signals within 500kb of the previous variant. A 500kb interval was added to the beginning of the first signal, and the end of the last signal to establish the final boundary of the trans-ancestry locus ( <b>Extended Data Figure 2</b> ). As defined, a trans-ancestry locus may not have a single lead trans-ancestry variant, but may instead contain multiple trans-ancestry lead variants, one for each trait.

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1363 **Online Methods**

1364 **Study design and participants**

1365 This study included trait data from four glycemic traits: fasting glucose (FG), fasting insulin (FI), 2hr  
1366 post-challenge glucose (2hGlu), and glycated hemoglobin (HbA1c). The total number of contributing  
1367 cohorts ranged from 41 (2hGlu) to 131 (FG), and the maximum sample size for each trait ranged  
1368 from 85,916 (2hGlu) to 281,416 (FG) (**Supplementary Table 1**). Overall, European ancestry (EUR)  
1369 participants dominated the sample size for all traits, representing between 68.0% (HbA1c) to 73.8%  
1370 (2hGlu) of the overall sample size. African Americans (AA) represented between 1.7% (2hGlu) to  
1371 5.9% (FG) of participants; individuals of Hispanic ancestry (HISP) represented between 6.8% (FG) to  
1372 14.6% (2hGlu) of participants; individuals of East-Asian ancestry (EAS) represented between 9.9%  
1373 (2hGlu) to 15.4% (HbA1c) of participants; and South-Asian ancestry (SAS) individuals represented  
1374 between 0% (no contribution to 2hGlu) to 4.4% (HbA1c) of participants. Data from Ugandan  
1375 participants were only available for the HbA1c analysis and represented 2% of participants.

1376

1377 **Phenotypes**

1378 Analyses included data for FG and 2hGlu measured in mmol/l, FI measured in pmol/l, and HbA1c in  
1379 % [where possible, studies reported HbA1c as a National Glycohemoglobin Standardization Program  
1380 (NGSP) percent]. Similar to previous MAGIC efforts<sup>7</sup>, individuals were excluded if they had type 1 or  
1381 type 2 diabetes (defined by physician diagnosis); reported use of diabetes-relevant medication(s); or  
1382 had a FG  $\geq 7$  mmol/L, 2hGlu  $\geq 11.1$  mmol/L, or HbA1c  $\geq 6.5\%$ , as detailed in **Supplementary Table 1**.  
1383 2hGlu measures were obtained 120 minutes after a glucose challenge in an oral glucose tolerance  
1384 test (OGTT). Measures for FG and FI taken from whole blood were corrected to plasma level using  
1385 the correction factor 1.13<sup>80</sup>.

1386

1387 **Genotyping, quality control, and imputation**

1388 Each participating cohort performed study-level quality control, imputation, and association  
1389 analyses following a shared analysis plan. Cohorts were genotyped using commercially available  
1390 genome-wide arrays or the Illumina CardioMetaboChip (MetaboChip) array (**Supplementary Table**  
1391 **1**)<sup>81</sup>. Prior to imputation, each cohort performed stringent sample and variant quality control (QC) to  
1392 ensure only high-quality variants were kept in the genotype scaffold for imputation. Sample quality  
1393 control checks included removing samples with low call rate  $< 95\%$ , extreme heterozygosity, sex  
1394 mismatch with X chromosome variants, duplicates, first- or second-degree relatives (unless by  
1395 design), or ancestry outliers. Following sample QC, cohorts applied variant QC thresholds for call rate  
1396 ( $< 95\%$ ), Hardy-Weinberg Equilibrium (HWE)  $P < 1 \times 10^{-6}$ , and minor allele frequency (MAF). Full  
1397 details of QC thresholds and exclusions by participating cohort are available in **Supplementary Table**  
1398 **1**.

1399

1400 Imputation was performed up to the 1000 Genomes Project phase 1 (v3) cosmopolitan reference  
1401 panel<sup>82</sup>, with a small number of cohorts imputing up to the 1000 Genomes phase 3 panel<sup>19</sup> or  
1402 population-specific reference panels (**Supplementary Table 1**).

1403

1404 **Study level association analyses**

1405 Each of the glycemic traits (FG, natural log FI, and 2hGlu) were regressed on BMI (except HbA1c),  
1406 study-specific covariates, and principal components (unless implementing a linear mixed model).  
1407 Analyses for FG, FI, and 2hGlu were adjusted for BMI as we had previously shown this did not  
1408 materially affect results for FG and 2hGlu but improved our ability to detect FI-associated loci<sup>15</sup>. For  
1409 simplicity, we refer to the traits as FG, FI and 2hGlu. For a discussion on collider bias see  
1410 **Supplementary Note section 2c**. Both the raw and rank-based inverse normal transformed residuals  
1411 from the regression were tested for association with genetic variants using SNPTTEST<sup>23</sup> or  
1412 Mach2QtI<sup>83,84</sup>. Poorly imputed variants, defined as imputation  $r^2 < 0.4$  or INFO score  $< 0.4$ , were  
1413 excluded from downstream analyses (**Supplementary Table 1**). Following study level QC,

1414 approximately 12,229,036 variants (GWAS cohorts) and 1,999,204 variants (MetaboChip cohorts)  
1415 were available for analysis (**Supplementary Table 1**).

1416

### 1417 **Centralized quality control**

1418 Each contributing cohort shared their summary statistic results with the central analysis group who  
1419 performed additional QC using EasyQC<sup>85</sup>. Allele frequency estimates were compared to estimates  
1420 from 1000Gp1 reference panel<sup>82</sup>, and variants were excluded from downstream analyses if there  
1421 was a minor allele frequency difference > 0.2 for AA, EUR, HISP, and EAS populations against AFR,  
1422 EUR, MXL, and ASN populations from 1000 Genomes Phase 1, respectively, or a minor allele  
1423 frequency difference > 0.4 for SAS against EUR populations. At this stage, additional variants were  
1424 excluded from each cohort file if they met one of the following criteria: were tri-allelic; had a minor  
1425 allele count (MAC) < 3; demonstrated a standard error of the effect size  $\geq 10$ ; or were missing an  
1426 effect estimate, standard error, or imputation quality. All data that survived QC (approximately  
1427 12,186,053 variants from GWAS cohorts and 1,998,657 variants from MetaboChip cohorts) were  
1428 available for downstream meta-analyses.

1429

### 1430 **Single-ancestry meta-analyses**

1431 Single-ancestry meta-analyses were performed within each ancestry group using the fixed-effects  
1432 inverse variance meta-analysis implemented in METAL<sup>20</sup>. We applied a double-genomic control (GC)  
1433 correction<sup>15,86</sup> to both the study-specific GWAS results and the single-ancestry meta-analysis results.  
1434 Study-specific MetaboChip results were GC-corrected using 4,973 SNPs included on the MetaboChip  
1435 array for replication of associations with QT-interval, a phenotype not correlated with our glycemic  
1436 traits<sup>15</sup>.

1437

### 1438 **Identification of single-ancestry index variants**

1439 To identify distinct association index variants across each chromosome within each ancestry (**Table**  
1440 **1**), we performed approximate conditional analyses implemented in GCTA<sup>21</sup> using the --cojo-slc  
1441 option (autosomes) and distance-based clumping (X chromosome). Linkage disequilibrium (LD)  
1442 correlations for GCTA were estimated from a representative cohort from each ancestry: WGHS  
1443 (EUR); CHNS (EAS); SINDI (SAS); BioMe (AA); SOL (HISP) and Uganda (for itself). The results from  
1444 GCTA were comparable when using alternative cohorts for the LD reference. For any index variant  
1445 with a QC flag which caused reason for concern, we performed manual inspection of forest plots to  
1446 decide whether the signal was likely to be real (**Supplementary note**). Among 335 single-ancestry  
1447 index variants across all traits, this manual inspection was done for 40 signals of which 32 passed  
1448 and 8 failed after inspection. Thus, a total of 327 single-ancestry index variants passed and 8 failed.

1449

### 1450 **Trans-ancestry meta-analyses**

1451 To leverage power across all ancestries, we also conducted trait-specific trans-ancestry meta-  
1452 analysis by combining the single-ancestry meta-analysis results using MANTRA (**Supplementary**  
1453 **note**)<sup>87</sup>. We defined  $\log_{10}$ Bayes' Factor (BF) > 6 as genome-wide significant, approximately  
1454 comparable to  $P < 5 \times 10^{-8}$ .

1455

### 1456 **Manual curation of trans-ancestry lead variants**

1457 To ensure trans-ancestry lead variants were robust, we performed manual inspection of forest plots  
1458 by at least two authors, for any variants with flags indicating possible QC issues (**Supplementary**  
1459 **note**). Of 463 trans-ancestry lead variants across all traits, 184 passed without inspection, 131  
1460 passed after inspection, and 148 failed after inspection.

1461

### 1462 **Correlation in EAF and heterogeneity in effect sizes of TA lead variants across ancestries**

1463 For each pair of ancestries, we calculated Pearson's correlation in EAFs for each trans-ancestry lead  
1464 variant. The pairwise summarized heterogeneity of effect sizes between ancestries was then tested



1465 using the joint F-test of heterogeneity<sup>32</sup>. The test statistic is the sum of Cochran Q-statistics for  
1466 heterogeneity across all trans-ancestry signals. Under the null hypothesis, the statistics follows the  $\chi^2$   
1467 distribution with n degrees of freedom, where n is the number of the trans-ancestry lead variants.  
1468

#### 1469 **LD-pruned variant lists**

1470 Several downstream analyses (for example, genomic feature enrichment, genetic scores, and  
1471 estimation of variance explained by associated variants) require independent LD-pruned variants  
1472 ( $r^2 < 0.1$ ) to avoid double-counting variants which might otherwise be in LD with each other and that  
1473 do not provide additional “independent” evidence. Therefore, for these analyses we generated  
1474 different lists of either TA or single-ancestry LD pruned ( $r^2 < 0.1$ ) variants, keeping in each case the  
1475 variant with the strongest evidence of association (**Supplementary Table 7**). Subsequently, we  
1476 combined TA and single-ancestry variant lists and conducted further LD pruning. For some analyses,  
1477 we took the TA pruned variant list and added single-ancestry signals if the LD  $r^2 < 0.1$ , while for others  
1478 we started with the single-ancestry pruned lists and supplemented with TA lead variants if the LD  
1479  $r^2 < 0.1$ . One exception was the list used for eQTL co-localizations, which included all single-ancestry  
1480 European signals (without LD pruning) and supplemented with any additional TA lead variants  
1481 (starting from the variants with the most significant P-values) in EUR LD  $r^2 < 0.1$  with any of the  
1482 variants already in list, and that reached at least  $P < 1 \times 10^{-5}$  in the European ancestry meta-analysis.  
1483

#### 1484 **Trait variance explained by associated loci**

1485 To determine how much of the phenotypic variance of each trait could be explained by the  
1486 corresponding trait-associated loci, variants were combined in a series of weighted genetic scores  
1487 (GS). The analysis was performed in a subset of the cohorts included in the discovery GWAS (with  
1488 representation from each ancestry) and in a smaller number of independent cohorts (European  
1489 ancestry only). Up to three different GS were derived per trait (and for each ancestry) in order to  
1490 evaluate the potential for the trans-ancestry meta-GWAS identified loci to provide additional  
1491 information above and beyond that contributed by the ancestry-specific meta-analysis results. These  
1492 GS comprised: List A - single-ancestry signals; List B - single-ancestry signals plus trans-ancestry  
1493 signals; and List C - trans-ancestry signals plus single-ancestry signals (**Supplementary Table 7**). In  
1494 the case of the European ancestry cohorts that contributed to the GWAS, we employed the method  
1495 of Nolte *et al.*<sup>33</sup> to adjust the effect sizes (betas) from the GWAS for the contribution of that cohort,  
1496 providing sets of cohort-specific effect sizes that were then used to generate the GS. The association  
1497 between each GS and its corresponding trait was tested by linear regression and the adjusted  $R^2$   
1498 from the model extracted as an estimate of the variance explained.  
1499

1500

#### 1501 **Transferability of European ancestry-derived polygenic scores (PGS) across ancestries**

1502 We used the PRS-CSauto<sup>34</sup> software to first build European ancestry-derived PGS for each glycemic  
1503 trait (FG, FI, 2hGlu, HbA1c) on the basis of summary statistics. However, PRS-CSauto does not  
1504 perform well when the training dataset is relatively small and the genetic architecture is sparse<sup>34</sup>.  
1505 Consequently, 2hGlu was excluded from this analysis. For each trait, to obtain European ancestry  
1506 training and test datasets, we first removed all cohorts only genotyped on the MetaboChip which  
1507 were not included in this analysis. From the remaining cohorts we then removed five of the largest  
1508 European cohorts contributing to the respective European ancestry meta-analysis. For each trait,  
1509 these five cohorts were meta-analyzed and used as the European ancestry test dataset.  
1510 Subsequently, the remaining European ancestry cohorts were also meta-analyzed and used as the  
1511 European ancestry training dataset. For each of the other ancestries, cohorts only genotyped on the  
1512 MetaboChip were also removed, and the remaining cohorts were meta-analyzed, and used as the  
1513 non-European ancestry test datasets. Variants with MAF  $< 0.05$  or missing in over half of the  
1514 individuals in the training dataset were removed<sup>34,88</sup>. The PGS for each trait was built using PRS-  
1515 CSauto with default settings<sup>34</sup> with the effect size estimates based on the European training dataset

1516 being revised based on an LD reference panel matching the test dataset. The proportion of the trait  
1517 variance explained by the European ancestry-derived PGS ( $R^2$ ) was estimated using the R package  
1518 “gtx”<sup>89</sup> based on the revised effect sizes and summary statistics from the test dataset for each  
1519 ancestry.

1520

1521

### 1522 **Fine-mapping**

1523 Of the 242 loci identified in this study, 237 were autosomal loci which we took forward for fine-  
1524 mapping (**Supplementary Table 2**). We used the Bayesian fine-mapping method FINEMAP<sup>90</sup> (version  
1525 1.1) to refine association signals and attempt to identify likely causal variants at each locus.

1526 FINEMAP estimates the maximum number of causal variants at each locus, calculates the posterior  
1527 probability of each variant being causal, and proposes the most likely configuration of causal  
1528 variants. The posterior probabilities of the configurations in each locus were used to construct 99%  
1529 credible sets.

1530

1531 We performed both single-ancestry and trans-ancestry fine-mapping. In both analyses, only data  
1532 from cohorts genotyped on GWAS arrays were used, and analyses were limited to trans-ancestry  
1533 lead variants and other single-ancestry lead variants present in at least 90% of the samples for each  
1534 trait. For the single-ancestry fine-mapping, FINEMAP estimates the number of causal variants in a  
1535 region up to a maximum number, which we set to be two plus the number of distinct signals  
1536 identified from the GCTA signal selection. FINEMAP uses single-ancestry and trait-specific z-scores  
1537 from the fixed-effect meta-analysis in METAL<sup>20</sup> and an ancestry-specific LD reference, which we  
1538 created from a subset of cohorts (combined sample size > 30% of the sample size for that ancestry),  
1539 weighting each cohort by sample size. In the trans-ancestry fine-mapping, FINEMAP was similarly  
1540 used to estimate the number of causal variants starting with two, and trait-specific z-scores and LD  
1541 maps were generated from the sample size weighted average of those used in the single-ancestry  
1542 fine-mapping. The maximum number of causal variants was iteratively increased by one until it was  
1543 larger than the number of causal variants supported by data (Bayes factor), which was the estimated  
1544 maximum number of causal variants used in the final run of fine-mapping analysis.

1545

1546 To compare fine-mapping results obtained from the single-ancestry and trans-ancestry efforts,  
1547 analyses were limited to fine-mapping regions with evidence for a single likely causal variant in both,  
1548 enabling a straightforward comparison of credible sets (**Supplementary note**). To ensure any  
1549 difference in the fine-mapping results was not driven by different sets of variants being present in  
1550 the different analyses, we repeated the single-ancestry fine-mapping limited to the same set of  
1551 variants used in the trans-ancestry fine-mapping. The fine-mapping resolution was assessed based  
1552 on comparisons of the 99% credible sets in terms of number of variants included in the set, and  
1553 length of the region. To assess whether the improvement in the trans-ancestry fine-mapping was  
1554 due to differences in LD, increased sample size, or both, we repeated the trans-ancestry fine-  
1555 mapping mimicking the sample size present in the single-ancestry fine-mapping by dividing the  
1556 standard errors by the square root of the sample size ratio and compared the results with those  
1557 from the single-ancestry fine-mapping.

1558

### 1559 **Functional Annotation of trait-associated variants**

1560

#### 1561 ***HbA1c signal classification***

1562 There were 218 HbA1c-associated signals from either the single-ancestry (i.e. all GCTA-signals from  
1563 any ancestry) or trans-ancestry meta-analyses. To classify these signals in terms of their likely mode  
1564 of action (i.e., glycemic, erythrocytic, or other<sup>7</sup>), we examined association summary statistics for the  
1565 lead variants at the 218 signals in other large European datasets for 19 additional traits: three  
1566 glycemic traits from this study (FG, 2hGlu and FI); seven mature red blood cell (RBC) traits<sup>91,92</sup> (red

1567 blood cell count, mean corpuscular volume, hematocrit, mean corpuscular hemoglobin, mean  
1568 corpuscular hemoglobin concentration, hemoglobin concentration and red cell distribution width);  
1569 five reticulocyte traits (reticulocyte count, reticulocyte fraction of red cells, immature fraction of  
1570 reticulocytes, high light scatter reticulocyte count and high light scatter percentage of red cells)<sup>91,92</sup>,  
1571 and four iron traits (serum iron, transferrin, transferrin saturation and ferritin)<sup>93</sup>. Of the 218 HbA1c  
1572 signals, data were available for the lead (n=183) or proxy (European LD  $r^2 > 0.8$ , n = 8) variants at 191  
1573 signals.

1574

1575 The additional traits were clustered using hierarchical clustering to ensure biologically related traits  
1576 would cluster together (**Supplementary note**). We then used a non-negative matrix factorization  
1577 (NMF)<sup>94</sup> process to cluster the HbA1c signals. Each cluster was labelled as glycemic, reticulocyte,  
1578 mature RBC, or iron related based on the strength of association of signals in the cluster to the  
1579 glycemic, reticulocyte, mature RBC and iron traits (**Supplementary note**). To verify that our cluster  
1580 naming was correct, we used HbA1c association results conditioned on either FG or iron traits, or  
1581 type 2 diabetes association results (**Supplementary note**).

1582

### 1583 ***HbA1c genetic risk scores (GRSs) and type 2 diabetes (T2D) risk***

1584 We constructed GRS for each cluster of HbA1c-associated signals (based on hard clustering) and  
1585 tested the association of each cluster with T2D risk using samples from the UK Biobank. Pairs of  
1586 HbA1c signals in LD (EUR  $r^2 > 0.10$ ) were LD pruned by removing the signal with the less significant *P*-  
1587 value of association with HbA1c. The GRS for each cluster was calculated based on the logarithm of  
1588 odds ratios from the latest T2D study summary statistics<sup>95</sup> and UK Biobank genotypes imputed to the  
1589 Haplotype Reference Consortium<sup>19</sup>. From 487,409 UK Biobank samples (age between 46 and 82  
1590 years, and 55% female), we excluded participants for the following reasons: 373 with mismatched  
1591 sex; 9 not used in the kinship calculation; 78,365 non-European ancestry individuals; and 138,504  
1592 with missing T2D status, age, or sex information. We further removed 26,896 related participants  
1593 (kinship > 0.088, preferentially removing individuals with the largest number of relatives and  
1594 controls where a T2D case was related to a control). T2D cases were defined by: (i) a history of  
1595 diabetes without metformin or insulin treatment, (ii) self-reported diagnosis of T2D, or (iii) diagnosis  
1596 of T2D in a national registry (N = 17,022, age between 47 and 79 years, and 36% female). Controls  
1597 were participants without a history of T2D (N = 226,240, age between 46 and 82 years, and 56%  
1598 female). We tested for association between each GRS and T2D using logistic regression including  
1599 covariates for age, sex, and the first five principal components. Significance of association was  
1600 evaluated by a bootstrap approach to incorporate the variance of each HbA1c associated signal in  
1601 the T2D summary data. To do this, we generated the GRS of each cluster 200 times by resampling  
1602 the logarithm of odds ratio of each signal with T2D. For each non-glycemic class that had a GRS  
1603 significantly associated with T2D, we performed sensitivity analyses to evaluate whether the  
1604 association was driven from variants that also belonged to a glycemic cluster when using a soft  
1605 clustering approach (the signals were classified as also glycemic in the soft clustering or had an  
1606 association  $P \leq 0.05$  with any of the three glycemic traits).

1607

### 1608 ***Chromatin states***

1609 To identify genetic variants within association signals that overlapped predicted chromatin states,  
1610 we used a previously published, 13 chromatin state model that included 31 diverse tissues, including  
1611 pancreatic islets, skeletal muscle, adipose, and liver<sup>39</sup>. Briefly, this model was generated from  
1612 cell/tissue ChIP-seq data for H3K27ac, H3K27me3, H3K36me3, H3K4me1, and H3K4me3, and input  
1613 control from a diverse set of publicly available data<sup>53,57,96,97</sup> using the ChromHMM program<sup>98</sup>. As  
1614 reported previously<sup>39</sup>, StrEs were defined as contiguous enhancer chromatin state (Active Enhancer  
1615 1 and 2, Genic Enhancer and Weak Enhancer) segments longer than 3kb<sup>57</sup>.

### 1616 ***Enrichment of genetic variants in genomic features***

1617 We used GREGOR (version 1.2.1) to calculate the enrichment of GWAS variants overlapping static  
1618 and StrEs<sup>56</sup>. For calculating the enrichment of glycemetic trait-associated variants in these annotations,  
1619 we used the filtered list of trait-associated variants as described above (**Supplementary Table 7**) as  
1620 input. For calculating the enrichment of sub-classified HbA1c variants, we included the list of loci  
1621 characterized as Glycemic, another list of loci characterized as Reticulocyte or mature Red Blood  
1622 Cell, collectively representing the red blood cell fraction, along with lists of iron related or  
1623 unclassified loci (**Supplementary Table 17**). We used the following parameters in GREGOR  
1624 enrichment analyses: European  $r^2$  threshold (for inclusion of variants in LD with the lead variant) =  
1625 0.8, LD window size = 1 Mb, and minimum neighbour number = 500.

1626

1627 We used fGWAS (version 0.3.6)<sup>58</sup> to calculate enrichment of glycemetic trait-associated variants in  
1628 static and StrE annotations using summary level GWAS results. We used the default fGWAS  
1629 parameters for enrichment analyses for individual annotations for each trait. For each annotation,  
1630 the model provided the natural log of maximum likelihood estimate of the enrichment parameter.  
1631 Annotations were considered as significantly enriched if the log<sub>2</sub> (parameter estimate) and  
1632 respective 95% confidence intervals were above zero or significantly depleted if the log<sub>2</sub> (parameter  
1633 estimate) and respective 95% confidence intervals were below zero.

1634

1635 We tested enrichment of trait-associated variants in static and StrE annotations with GARFIELD  
1636 (v2)<sup>59</sup>. We formatted annotation overlap files as required by the tool; prepared input data at two  
1637 GWAS thresholds - of  $1 \times 10^{-5}$  and a more stringent  $1 \times 10^{-8}$  by pruning and clumping with default  
1638 parameters (garfield-prep-chr script). We calculated enrichment in each individual annotation using  
1639 garfield-test.R with  $-c$  option set to 0. We also calculated the effective number of annotations using  
1640 the garfield-Meff-Padj.R script. We used the effective number of annotations for each trait to obtain  
1641 Bonferroni corrected significance thresholds for enrichment for each trait.

1642

#### 1643 ***eQTL analyses***

1644 To aid in the identification of candidate casual genes at the European-only and trans-ancestry  
1645 association signals, we examined whether any of the lead variants associated with glycemetic traits  
1646 (**Supplementary Table 7**) were also associated with expression level (FDR < 5%) of nearby transcripts  
1647 located within 1 Mb in existing eQTL data sets of blood, subcutaneous adipose, visceral adipose,  
1648 skeletal muscle, and pancreatic islet samples<sup>60,61,99-102</sup>. LD was estimated from the collected cohort  
1649 pairwise LD information, where available, else from the European samples in 1000G phase 3. GWAS  
1650 and eQTL signals likely co-localize when the GWAS variant and the variant most strongly associated  
1651 with the expression level of the corresponding transcript (eSNP) exhibit high pairwise LD ( $r^2 > 0.8$ ;  
1652 1000 Genomes Phase 3, EUR). At these signals, we conducted reciprocal conditional analyses to test  
1653 association between the GWAS variant and transcript level when the eSNP was also included in the  
1654 model, and vice versa. We report GWAS and eQTL signals as co-localized if the association for the  
1655 eSNP was not significant (FDR  $\geq 5\%$ ) when conditioned on the GWAS variant; we also report signals  
1656 from the eQTLGen whole blood meta-analysis data that meet only the LD threshold because  
1657 conditional analysis was not possible.

1658

#### 1659 ***Tissue and gene-set analysis***

1660 We performed enrichment analysis using DEPICT (Data-driven Expression-Prioritized Integration for  
1661 Complex Traits) version 3, specifically developed for 1000 Genomes Project imputed meta-analysis  
1662 data<sup>103</sup> to identify cell types and tissues in which genes at trait-associated variants were strongly  
1663 expressed, and to detect enrichment of gene-sets or pathways. DEPICT data included human gene  
1664 expression data for 19,987 genes in 10,968 reconstituted gene sets, and 209 tissues/cell types.  
1665 Because gene expression data in DEPICT is based on European samples and LD, we selected trait-  
1666 associated variants with  $P < 10^{-5}$  in the European meta-analysis and tested for enrichment of signals in  
1667 each reconstituted gene-set, and each tissue or cell type. Enrichment results with a false discovery

1668 rate (FDR)<0.05 were considered significant. We ran DEPICT based on association results for all traits  
1669 among: (i) cohorts with genome-wide data, or (ii) all cohorts (genome-wide and Metabochip  
1670 cohorts). Because results were broadly consistent between the two approaches, we present results  
1671 from the analysis that contained all cohorts as it had greater statistical power.

1672

### 1673 **Statistics and reproducibility**

1674

#### 1675 *Sample size*

1676 No statistical method was used to predetermine sample size. We aimed to bring together the largest  
1677 possible sample size with GWAS data from individuals of diverse ancestries (European, Hispanic,  
1678 African American, East Asian, South Asian and sub-Saharan African) without diabetes and with data  
1679 for one or more of the following traits: fasting glucose, fasting insulin, 2hr post-challenge glucose,  
1680 and glycated hemoglobin. The sample sizes were 281,416 (FG), 213,650 (FI), 215,977 (HbA1c) and  
1681 85,916 (2hGlu) (**Supplementary Table 1**). Our sample size was sufficiently powered to detect  
1682 common variant associations with each of the glycemc traits and was able to detect associations at  
1683 242 loci.

1684

#### 1685 *Randomization/ Blinding*

1686 This is a study of continuous traits therefore there were no experiments to randomize and there was  
1687 no “outcome” to which investigators needed to be blinded to.

1688

#### 1689 *Data exclusions*

1690 Prior to conducting this study, we identified reasons for which data should be excluded from the  
1691 analysis at either the cohort or summary level; these exclusions are as follows. Sample quality  
1692 control checks included removing samples with low call rate < 95%, extreme heterozygosity, sex  
1693 mismatch with X chromosome variants, duplicates, first- or second-degree relatives (unless by  
1694 design), or ancestry outliers. Following sample QC, cohorts applied variant QC thresholds for call rate  
1695 (< 95%), Hardy-Weinberg Equilibrium (HWE)  $P < 1 \times 10^{-6}$ , and minor allele frequency (MAF). Full  
1696 details of QC thresholds and exclusions by participating cohort are available in **Supplementary Table**  
1697 **1**. Each contributing cohort shared their summary statistic results with the central analysis group  
1698 who performed additional QC using EasyQC. Allele frequency estimates were compared to estimates  
1699 from 1000Gp1 reference panel, and variants were excluded from downstream analyses if there was  
1700 a minor allele frequency difference > 0.2 for AA, EUR, HISP, and EAS populations against AFR, EUR,  
1701 MXL, and ASN populations from 1000 Genomes Phase 1, respectively, or a minor allele frequency  
1702 difference > 0.4 for SAS against EUR populations. At this stage, additional variants were excluded  
1703 from each cohort file if they met one of the following criteria: were tri-allelic; had a minor allele  
1704 count (MAC) < 3; demonstrated a standard error of the effect size  $\geq 10$ ; imputation  $r^2 < 0.4$  or INFO  
1705 score < 0.4; or were missing an effect estimate, standard error, or imputation quality.

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#### 1708 **Data Availability**

1709 Ancestry-specific and overall meta-analysis summary level results are available through the MAGIC  
1710 website (<https://www.magicinvestigators.org/>). Summary statistics are also available through the  
1711 GWAS catalogue (<https://www.ebi.ac.uk/gwas/>) with the following accession codes: GCST90002225,  
1712 GCST90002226, GCST90002227, GCST90002228, GCST90002229, GCST90002230, GCST90002231,  
1713 GCST90002232, GCST90002233, GCST90002234, GCST90002235, GCST90002236, GCST90002237,  
1714 GCST90002238, GCST90002239, GCST90002240, GCST90002241, GCST90002242, GCST90002243,  
1715 GCST90002244, GCST90002245, GCST90002246, GCST90002247, and GCST90002248.

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#### 1717 **References for Methods**

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1719 80 D'Orazio, P. *et al.* Approved IFCC recommendation on reporting results for blood  
1720 glucose (abbreviated). *Clinical chemistry* **51**, 1573-1576,  
1721 doi:10.1373/clinchem.2005.051979 (2005).

1722 81 Voight, B. F. *et al.* The metabochip, a custom genotyping array for genetic studies of  
1723 metabolic, cardiovascular, and anthropometric traits. *PLoS genetics* **8**, e1002793,  
1724 doi:10.1371/journal.pgen.1002793 (2012).

1725 82 Abecasis, G. R. *et al.* An integrated map of genetic variation from 1,092 human  
1726 genomes. *Nature* **491**, 56-65, doi:10.1038/nature11632 (2012).

1727 83 Li, Y., Willer, C. J., Ding, J., Scheet, P. & Abecasis, G. R. MaCH: using sequence and  
1728 genotype data to estimate haplotypes and unobserved genotypes. *Genetic  
1729 epidemiology* **34**, 816-834, doi:10.1002/gepi.20533 (2010).

1730 84 Pei, Y. F., Zhang, L., Li, J. & Deng, H. W. Analyses and comparison of imputation-  
1731 based association methods. *PloS one* **5**, e10827, doi:10.1371/journal.pone.0010827  
1732 (2010).

1733 85 Winkler, T. W. *et al.* Quality control and conduct of genome-wide association meta-  
1734 analyses. *Nature protocols* **9**, 1192-1212, doi:10.1038/nprot.2014.071 (2014).

1735 86 Devlin, B. & Roeder, K. Genomic control for association studies. *Biometrics* **55**, 997-  
1736 1004 (1999).

1737 87 Morris, A. P. Transethnic meta-analysis of genomewide association studies. *Genetic  
1738 epidemiology* **35**, 809-822, doi:10.1002/gepi.20630 (2011).

1739 88 Bulik-Sullivan, B. K. *et al.* LD Score regression distinguishes confounding from  
1740 polygenicity in genome-wide association studies. *Nature genetics* **47**, 291-295,  
1741 doi:10.1038/ng.3211 (2015).

1742 89 Dastani, Z. *et al.* Novel loci for adiponectin levels and their influence on type 2  
1743 diabetes and metabolic traits: a multi-ethnic meta-analysis of 45,891 individuals.  
1744 *PLoS genetics* **8**, e1002607, doi:10.1371/journal.pgen.1002607 (2012).

1745 90 Benner, C. *et al.* FINEMAP: efficient variable selection using summary data from  
1746 genome-wide association studies. *Bioinformatics (Oxford, England)* **32**, 1493-1501,  
1747 doi:10.1093/bioinformatics/btw018 (2016).

1748 91 Astle, W. J. *et al.* The Allelic Landscape of Human Blood Cell Trait Variation and Links  
1749 to Common Complex Disease. *Cell* **167**, 1415-1429.e1419,  
1750 doi:10.1016/j.cell.2016.10.042 (2016).

1751 92 Canela-Xandri, O., Rawlik, K. & Tenesa, A. An atlas of genetic associations in UK  
1752 Biobank. *Nature genetics* **50**, 1593-1599, doi:10.1038/s41588-018-0248-z (2018).

1753 93 Benyamin, B. *et al.* Novel loci affecting iron homeostasis and their effects in  
1754 individuals at risk for hemochromatosis. *Nature communications* **5**, 4926,  
1755 doi:10.1038/ncomms5926 (2014).

1756 94 Binesh, N. & Rezghi, M. Fuzzy clustering in community detection based on  
1757 nonnegative matrix factorization with two novel evaluation criteria. *Applied Soft  
1758 Computing* **69**, 689-703 (2018).

1759 95 Scott, R. A. *et al.* An Expanded Genome-Wide Association Study of Type 2 Diabetes in  
1760 Europeans. *Diabetes* **66**, 2888-2902, doi:10.2337/db16-1253 (2017).

1761 96 Ernst, J. *et al.* Mapping and analysis of chromatin state dynamics in nine human cell  
1762 types. *Nature* **473**, 43-49, doi:10.1038/nature09906 (2011).

1763 97 Mikkelsen, T. S. *et al.* Comparative epigenomic analysis of murine and human  
1764 adipogenesis. *Cell* **143**, 156-169, doi:10.1016/j.cell.2010.09.006 (2010).

1765 98 Ernst, J. & Kellis, M. ChromHMM: automating chromatin-state discovery and  
1766 characterization. *Nature methods* **9**, 215-216, doi:10.1038/nmeth.1906 (2012).  
1767 99 Battle, A., Brown, C. D., Engelhardt, B. E. & Montgomery, S. B. Genetic effects on  
1768 gene expression across human tissues. *Nature* **550**, 204-213,  
1769 doi:10.1038/nature24277 (2017).  
1770 100 Zhernakova, D. V. *et al.* Identification of context-dependent expression quantitative  
1771 trait loci in whole blood. *Nature genetics* **49**, 139-145, doi:10.1038/ng.3737 (2017).  
1772 101 Westra, H. J. *et al.* Systematic identification of trans eQTLs as putative drivers of  
1773 known disease associations. *Nature genetics* **45**, 1238-1243, doi:10.1038/ng.2756  
1774 (2013).  
1775 102 Joehanes, R. *et al.* Integrated genome-wide analysis of expression quantitative trait  
1776 loci aids interpretation of genomic association studies. *Genome biology* **18**, 16,  
1777 doi:10.1186/s13059-016-1142-6 (2017).  
1778 103 Pers, T. H. *et al.* Biological interpretation of genome-wide association studies using  
1779 predicted gene functions. *Nature communications* **6**, 5890,  
1780 doi:10.1038/ncomms6890 (2015).  
1781