

The Trans-Ancestral Genomic Architecture of Glycaemic Traits

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453

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455

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458

459

460 **Abstract**

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

473 Fasting glucose (FG), 2h-glucose post-challenge (2hGlu), and glycated haemoglobin (HbA1c) are
474 glycaemic traits used to diagnose diabetes¹. In addition, HbA1c is the most commonly used
475 biomarker to monitor glucose control in patients with diabetes. Fasting insulin (FI) reflects a
476 combination of **insulin secretion and** insulin resistance, both components of type 2 diabetes (T2D),
477 and insulin clearance². Collectively, all four of these glycaemic traits can be useful to better
478 understand T2D pathophysiology³⁻⁵ **and** are useful measures of cardiometabolic health as they are
479 associated with cardiometabolic outcomes even within the non-diabetic range, albeit modestly so⁶.

480

481 To date, genome-wide association studies (GWAS) and analysis of next-generation targeted arrays
482 (Metabochip and exome array) have identified >120 loci associated with glycaemic traits in
483 individuals without diabetes⁷⁻¹⁵. However, despite considerable differences in the prevalence of T2D
484 risk factors across ancestries¹⁶⁻¹⁸, most glycaemic trait GWAS in individuals without diabetes have
485 insufficient representation of individuals of non-European ancestry and limited resolution for fine-
486 mapping of causal variants and effector transcript identification. Here, we present large-scale trans-
487 ancestry discovery meta-analyses of GWAS for four glycaemic traits (FG, 2hGlu, FI, and HbA1c) in
488 individuals without diabetes with genotype imputation to the 1000 Genomes Project reference
489 panel phase 1 version 3¹⁹. Our aims were to identify additional glycaemic trait-associated loci;
490 investigate the portability of loci and genetic scores across ancestries; leverage differences in effect
491 allele frequency (EAF), effect size, and linkage disequilibrium (LD) across diverse populations to
492 conduct fine-mapping and aid causal variant/effector transcript identification; and compare and
493 contrast the genetic architecture of these four glycaemic traits to further elucidate their underlying
494 biology and gain insights into pathophysiological pathways implicated in T2D.

495

496 **Results**

497

497 **Study design, lead variant, index variant and trans-ancestry locus definitions**

498

498 To identify loci associated with glycaemic traits FG, 2hGlu, FI, and HbA1c, we aggregated GWAS in up
499 to 281,416 individuals without diabetes, ~30% of whom were of non-European ancestry [13% East
500 Asian, 7% Hispanic, 6% African-American, 3% South Asian, and 2% sub-Saharan African (Ugandan -
501 data only available for HbA1c)]. Prior to meta-analysis each contributing cohort imputed data to the
502 1000 Genomes Project reference panel (phase 1 v3, March 2012, or later; **Methods, Supplementary**
503 **Table 1, Supplementary Figure 1**). In total, up to ~49.3 million variants were directly genotyped or
504 imputed, with between 38.6 million (2hGlu) and 43.5 million variants (HbA1c) available for analysis
505 after exclusions based on minor allele count (MAC < 3) and imputation quality (imputation r^2 or INFO
506 score < 0.40) in each cohort. As we had previously found adjusting for body mass index (BMI)
507 provided similar results for FG and 2hGlu, but aided in new locus discovery for FI¹⁵, here we
508 conducted analyses for FG, 2hGlu and FI adjusted for BMI, but for simplicity these traits are
509 abbreviated as FG, 2hGlu and FI (**Methods**).

510

511 We first performed trait-specific fixed-effect meta-analyses *within* each ancestry using METAL²⁰. We
512 defined “single-ancestry lead” variants as the strongest trait-associated variants ($P < 5 \times 10^{-8}$) within a
513 1Mb region in a particular ancestry (**Glossary box**). Within each ancestry and each autosome, we
514 used approximate conditional analyses in GCTA^{21,22}, to identify distinct “single-ancestry index
515 variants” ($P < 5 \times 10^{-8}$) that exert conditionally distinct effects on the trait (**Glossary Box, Methods,**
516 **Supplementary Figure 2**). Overall, this approach identified 124 distinct FG, 15 2hGlu, 48 FI and 139
517 HbA1c variants that were significant in at least one ancestry (**Supplementary Table 2**).

518

519 Next, we conducted trait-specific *trans-ancestry* meta-analyses of ancestry-specific results using
520 MANTRA (**Methods, Supplementary Table 1, Supplementary Figures 1 and 3**) to identify genome-
521 wide significant “trans-ancestry lead variants”, defined as the most significant trait-associated
522 variant across all ancestries (\log_{10} Bayes Factor [BF] > 6, equivalent to $P < 5 \times 10^{-8,23}$) (**Glossary box,**

523 **Methods**). Here, we present trans-ancestry results based on data from all participating cohorts as
524 our primary results (**Supplementary Table 2**).

525

526 Causal variants are expected to affect multiple related glycaemic traits and may be shared across
527 ancestries. Therefore, we combined all single-ancestry lead variants, single-ancestry index variants,
528 and/or trans-ancestry lead variants (for any trait) mapping within 500Kb of each other, into a single
529 “trans-ancestry locus” that was bounded by a 500Kb flanking sequence (**Glossary Box**). As defined, a
530 trans-ancestry locus may contain multiple causal variants affecting one or more glycaemic traits,
531 exerting their effect in one or more ancestry.

532

533 **Glycaemic trait locus discovery**

534 In the trans-ancestry meta-analyses, we observed genome-wide significant associations at 235 trans-
535 ancestry loci, of which 59 contained trans-ancestry lead variants for more than one trait. In addition,
536 we identified seven “single-ancestry loci” that did not contain any trans-ancestry lead variants
537 (**Glossary box, Supplementary Table 2**). Of the 242 trans-ancestry and single-ancestry loci, 99
538 (including 6 of the 7 single-ancestry) had not been previously associated with any of the four
539 glycaemic traits or with T2D, at the time of analysis (**Figure 1, Supplementary Figures 1 and 3,**
540 **Supplementary Table 3, Supplementary note**). However, based on the currently available largest
541 East Asian ancestry and trans-ancestry T2D GWAS meta-analyses²³⁻²⁷, the lead variants at 27/99
542 novel glycaemic trait loci have strong evidence of association with T2D ($P < 10^{-4}$; 13 loci with $P < 5 \times 10^{-8}$
543 ⁸), suggesting some of the novel loci are also important in diabetes pathophysiology (**Supplementary**
544 **Tables 2 and 4**).

545

546 Of the 99 novel loci, six were identified in a single ancestry (**Supplementary Table 3**). Three single-
547 ancestry loci were associated in individuals of non-European ancestry: (i) an African American
548 association for FG (lead variant rs61909476) near the gene *ETS1*, (ii) an African American association
549 for FI (lead variant rs12056334) near the gene *LOC100128993* (an uncharacterised RNA gene;
550 **Supplementary Note**), and (iii) a Hispanic association for FG (lead variant rs12315677) within the
551 gene *PIK3C2G* (**Supplementary Table 3**). The associations of rs61909476 and rs12315677 with FG are
552 noteworthy. The variant rs61909476 has an EAF of ~7% in African American, and 10-17% in all other
553 ancestries (**Supplementary Table 2**), but the effect on FG is only detectable in African American
554 individuals ($b=0.0812$ mmol/l, $SE=0.01$ mmol/l, $P=3.9 \times 10^{-8}$, all other ancestries $b=0-0.002$ mmol/l,
555 $se=0.003-0.017$ mmol/l, $p=0.44-0.95$, **Supplementary table 2, Supplementary Figure 4,**
556 **Supplementary note**). The nearest gene, *ETS1*, encodes a transcription factor which has been shown
557 to localize to insulin-positive cells in mouse islets, and its overexpression was shown to decrease
558 glucose-stimulated insulin secretion in mouse islets²⁸. Located within the *PIK3C2G* gene, rs12315677
559 has an 84% EAF in Hispanic and ranges from 70-94% in other ancestry populations, but is
560 significantly associated with FG only in our Hispanic GWAS ($b=0.0387$ mmol/l, $SE=0.0075$ mmol/l,
561 $P=4.0 \times 10^{-8}$) compared with other ancestries ($b=-0.0128-0.010$ mmol/l, $SE=0.003-0.018$ mmol/l,
562 $P=0.14-0.76$) (**Supplementary Figure 5, Supplementary note**). *PIK3C2G* has been shown to be a Rab5
563 effector which, when deleted in *Pik3c2g*^{-/-} mice, selectively inhibits *Akt2* activation and leads to a
564 phenotype characterised by reduced glycogen storage in the liver, hyperlipidaemia, adiposity, and
565 insulin resistance with increasing age, or after a high fat diet²⁹. Instances where the EAFs are similar
566 between populations, but the effect sizes differ, could be due to specific genotype-by-environment
567 or other genotype epistatic effects that differ across ancestries, or lower imputation accuracy in
568 ancestries with smaller sample sizes, although this would likely lead to deflated effect sizes and
569 imputation quality is good for these variants (average $r^2=0.81$). It is also possible that the variants
570 detected here are not themselves causal, but are in LD with ancestry-specific causal variants that are
571 not directly interrogated in our meta-analysis and that differ in frequency across ancestries. We
572 looked at data from 1000G in the cognate populations, but could not find evidence of rarer alleles in
573 those ancestries that may themselves be driving the association signals (**Supplementary Table 5**).

574 However, this does not preclude the possibility that other rarer variants exist which are not
575 represented in the 1000G populations. The final three single-ancestry loci were identified in
576 individuals of European ancestry, but without any evidence of association in the other ancestries
577 despite similar MAF, although this may be due to differences in power given the much smaller
578 sample sizes in non-European ancestries (**Supplementary Figures 6-8**).

579
580 Next, to investigate the contribution of non-European ancestry data to novel trans-ancestry locus
581 discovery, independent of the total sample size, we artificially boosted the sample size of the
582 European meta-analysis to match that of trans-ancestry meta-analysis by rescaling the standard
583 errors of allelic effect sizes (**Supplementary note**). Using this approach, we determined that 21 of
584 the novel trans-ancestry loci would not have been discovered with an equivalent sample size
585 comprised exclusively of European ancestry individuals (**Supplementary note**). Their discovery was
586 due to the higher EAF and/or larger effect size in non-European ancestry populations. In particular,
587 two loci (nearest genes *LINC00885* and *MIR4278*) contain East Asian and African American single-
588 ancestry lead variants, respectively, suggesting that these specific ancestries may be driving the
589 trans-ancestry discovery (**Supplementary Tables 2-3**). Combined with the three single-ancestry non-
590 European loci described above, our results show that 24% (24/99) of novel loci were discovered due
591 to the contribution of non-European ancestry participants, strengthening the argument for
592 extending genetic studies to larger samples sizes in diverse populations.

593 594 **Allelic architecture of glycaemic traits**

595 Trans-ancestry and single-ancestry loci comprised a range of association patterns, with most loci
596 harbouring one single-ancestry signal for any given trait (**Supplementary note**). However, 29 loci
597 contained multiple distinct index variants that did not fully overlap between ancestries. The most
598 complex locus we observed was in the region spanning *G6PC2*, which contained 14 distinct FG index
599 variants in the European single-ancestry meta-analysis. Of these, four are shared ($P < 5 \times 10^{-8}$) with
600 South Asian ancestry, two with East Asian ancestry, and two with Hispanic ancestry (**Supplementary**
601 **Figure 9**). The complexity of association signals at this locus is consistent with previous work that
602 also reported common variant (MAF > 5%) association signals and multiple rare variant (MAF ≤ 1%)
603 associations at this locus that influenced protein function by multiple mechanisms³⁰.

604
605 Combined, single-ancestry lead, single-ancestry index, and trans-ancestry lead variants increase the
606 number of established loci for FG to 102 (182 signals, 53 novel loci), FI to 66 (95 signals, 49 novel
607 loci), 2hGlu to 21 (28 signals, 11 novel loci), and HbA1c to 127 (218 signals, 62 novel loci)
608 (**Supplementary Table 2**) and demonstrate significant overlap across glycaemic traits
609 (**Supplementary Figure 10**). We also detected ($P < 0.05$ or $\log_{10}BF > 0$) the vast majority (~90%) of
610 previously established glycaemic trait association signals in our data, 70-88% of which attained
611 genome-wide significance in the current analyses (see further details in the **Supplementary Note**
612 and **Supplementary Table 6**). Given that analyses for FG, FI, and 2hGlu were performed adjusted for
613 BMI, we also confirmed that collider bias was not influencing discovery for more than 98% of our
614 results (**Supplementary note**)³¹.

615
616 Finally, as expected, given the greater power due to increased sample sizes, new association signals
617 tended to have smaller effect sizes and/or EAFs in European ancestry individuals (in whom this
618 analysis was conducted) compared to previously established signals (**Supplementary Figure 11**).

619 620 **Characterisation of trans-ancestry lead variants and European index variants across ancestries**

621 We next employed a series of complementary analyses to better understand the transferability of
622 trans-ancestry lead variants across all ancestries. For each trans-ancestry lead variant, we
623 investigated the pairwise EAF correlation between ancestries, as well as the pairwise summarised
624 heterogeneity of effect sizes between ancestries³² (**Methods and Supplementary Note**). In

625 agreement with population history and evolution, these results demonstrated considerable EAF
626 correlation ($\rho^2 > 0.70$) between European and Hispanic populations, European and South Asian
627 populations, and Hispanic and South Asian populations, consistent across all four traits, and
628 between African Americans and Ugandans for HbA1c (**Supplementary Figure 12**). Despite significant
629 EAF correlations, some pairwise comparisons exhibited strong evidence for effect size heterogeneity
630 between ancestries that was less consistent between traits (**Supplementary Figure 12**). However,
631 sensitivity analyses demonstrated that, across all comparisons, the evidence for heterogeneity is
632 driven by a small number of variants, with between 81.5% (for HbA1c) and 85.7% of trans-ancestry
633 lead variants (for FG) showing no evidence for trans-ancestry heterogeneity ($P > 0.05$)
634 (**Supplementary Note**).

635
636 We also took LD pruned European single-ancestry index variants and compared the direction of
637 effect of these variants in European ancestry individuals with that in other ancestries
638 (**Supplementary Note**). Consistent with the lack of heterogeneity in effect sizes, we saw >70%
639 concordance in the direction of effect for all traits into all ancestries, with the exception of HbA1c
640 into African Americans and Ugandans (**Supplementary Table 7**). Imperfect concordance between
641 ancestries could reflect lower power in non-European ancestry groups due to sample size or
642 variation in allele frequency, or could be explained by LD differences between index SNPs and causal
643 variants. For HbA1c, we hypothesized that lower concordance might also be a reflection of the
644 different pathways (glycaemic and non-glycaemic) through which variants can affect HbA1c levels,
645 particularly effects mediated via the red blood cell (RBC) where balancing selection can lead to
646 different associations in individuals of African ancestry⁷ (**Supplementary Note** and below).

647
648 To further investigate the potential utility of trans-ancestry analyses, and to evaluate whether larger
649 sample sizes might yield additional European ancestry signals that would be transferable across
650 ancestries, we extended these concordance analyses to the entire genome, clumping variants
651 mapping >1Mb apart (to eradicate the effect of LD in all ancestries) in different bins of association p-
652 values obtained from the European ancestry meta-analysis (**Methods**). Aside from the bins with the
653 weakest evidence for association in Europeans (i.e. in all bins with $P \leq 0.05$), we observed nominally
654 significant concordance in the direction of effects between European and other ancestries for all
655 traits except for 2hGlu, in which analyses were underpowered (**Supplementary Table 7**).

656
657 **Trait variance explained by associated loci**
658 The trait variance explained by genome-wide significant loci was assessed using the single-ancestry
659 lead and index variants only or a combination of single-ancestry and trans-ancestry variants
660 (**Supplementary Table 8**) with betas extracted from the relevant single-ancestry meta-analysis
661 results (**Methods**). The variance explained was assessed by linear regression in a subset of the
662 contributing cohorts (**Methods, Supplementary Tables 9-12**). In general, the optimal approach (i.e.
663 that which explained the most variance) was to begin with the trans-ancestry lead variants (based
664 on the MANTRA results) that have $P < 0.1$ in the relevant single-ancestry meta-analysis, then add in
665 all single-ancestry lead and index variants that are not in LD with the trans-ancestry variants ($LD\ r^2 <$
666 0.1) (List C) (**Supplementary Tables 9-12, Figure 2**). However, in the European ancestry cohorts there
667 was little gain from using trans-ancestry loci. Using this list of trans-ancestry lead variants
668 supplemented with single-ancestry signals, the mean variance in the trait distribution explained was
669 between 0.7% (2hGlu in EUR) and 6% (HbA1c in AA). In European ancestry studies, these estimates
670 represent an improvement (i.e. more variance explained) relative to previous estimates of 2.8% for
671 FG and 1.7% for HbA1c³³ (see further discussion in **Supplementary Note**).

672
673 **Transferability of European ancestry-derived polygenic scores across ancestries**
674 To investigate the transferability of polygenic scores across ancestries we used the PRS-CSauto
675 software³⁴ to first build polygenic scores for each glycaemic trait (FG, FI, 2hGlu and HbA1c) based on

676 European ancestry data. However, the training set for 2hGlu was too small so this trait was excluded
677 (**Methods**). We have used the term polygenic scores (PGS) as strictly speaking for continuous traits
678 they are not risk scores. To build the PGS, for each trait we first removed five of the largest European
679 cohorts contributing to the respective European ancestry meta-analysis (**Methods**). These five
680 cohorts were meta-analysed and used as our European ancestry test dataset, for each trait. The
681 remaining European ancestry cohorts were also meta-analysed and used as the training dataset
682 from which we derived a PGS for each trait (**Methods**). We used PRS-CSauto to revise the effect size
683 estimates for the variants in the score (obtained from the training European datasets) based on the
684 LD of the test population (**Methods**). Unfortunately, PRS-CSauto does not have LD reference panels
685 for South Asian or Hispanic ancestry and as such we were unable to test the transferability of the
686 PGS into those populations. The “gtx” package³⁵ (**Methods**) was used to obtain the R^2 for each test
687 population (**Figure 3, Supplementary Table 13**). In line with observations from other complex
688 traits³⁶, the European ancestry-derived PGS had greater predictive power into test data of European
689 ancestry than other ancestry groups.

690

691 **Fine-mapping**

692 Of the 242 identified loci, 231 were autosomal trans-ancestry loci and six were autosomal single-
693 ancestry loci, which we took forward for fine-mapping (**Supplementary Table 2**). Due to the absence
694 of LD maps from adequately sized populations, fine-mapping was not attempted for the 5 loci (4
695 trans-ancestry and 1 single-ancestry) mapping to the X chromosome. Using FINEMAP with ancestry-
696 specific LD and an average LD matrix across ancestries, we conducted fine-mapping both within
697 single-ancestries (161 autosomal loci with single-ancestry lead variants⁹⁹⁹) and across ancestries
698 (231 autosomal trans-ancestry loci) for each trait (**Methods**). Because 59 of the 231 trans-ancestry
699 loci were associated with more than one trait, we conducted trans-ancestry fine-mapping for a total
700 of 305 locus-trait associations. Of these 305 locus-trait combinations, FINEMAP estimated the
701 presence of a single causal variant responsible for the association at 186 loci (61%), while multiple
702 distinct causal variants were implicated at 126 loci (39%), for a total of 464 causal variants (**Figure**
703 **4A**).

704

705 *Credible sets for causal variants*

706 At each locus, we next constructed credible sets (CS) for each causal variant that account for $\geq 99\%$
707 of the posterior probability of association (PPA). We identified 21 locus-trait associations (at 19 loci)
708 for which the 99% CS included a single variant, and we highlight five examples below. (**Methods,**
709 **Supplementary Note, Figure 4B, Supplementary Table 14**).

710

711 We highlight two positive controls which provide confidence in the results. At one locus near
712 *MTNR1B*, rs10830963 (PPA >0.999 , for both HbA1c and FG), located in an *MTNR1B* intron, has shown
713 allelic differences in enhancer activity and transcription factor binding³⁷. An additional FG-
714 associated locus near *SIX3*, rs12712928 (PPA=0.997) has shown allelic differences in transcriptional
715 activity, transcription factor binding, and association with islet expression levels of nearby genes
716 *SIX3* and *SIX2*^{38,39}. The EAF and effect size of this variant is larger in EAS than in other ancestries
717 (heterogeneity p-value= 7.2×10^{-8}), which is driving the association at this locus.

718

719 Next, we highlight three novel findings. At a locus near *PFKM* associated with HbA1c, trans-ancestry
720 fine-mapping identified rs12819124 (PPA >0.999) as the likely causal variant. This variant has been
721 previously associated with mean corpuscular haemoglobin⁴⁰, suggesting an effect of this locus on
722 HbA1c is via the RBC. We note that this locus also harbours an association with FI in European and
723 trans-ancestry meta-analyses, although it appears to be distinct from the HbA1c signal based on
724 distance and LD. Fine-mapping of the nearby FI signal in European ancestry populations identified
725 rs111264094 (PPA=0.994) as the likely causal variant (**Supplementary Figures 13-14**). rs111264094 is
726 a low frequency variant in Europeans (EAF=0.025) that is monomorphic or rare in other ancestries, is

727 located >600 kb from HbA1c-associated variant rs12819124, and is in low LD with rs12819124 in
728 European ancestry populations ($r^2 < 0.1$), which supports the hypothesis of two distinct signals (one
729 for FI and one HbA1c) at this locus.

730

731 At the *HBB* locus, we identify rs334 (PPA>0.999; Glu7Val) as the likely causal variant associated with
732 HbA1c. rs334 is a causal variant of sickle cell anaemia⁴¹, with previously reported associations with
733 urinary albumin-to-creatinine ratio in Caribbean Hispanic individuals⁴², severe malaria in a
734 Tanzanian study population⁴³, haematocrit and mean corpuscular volume in Hispanic/Latino
735 populations⁴⁴, and more recently with RBC distribution in Ugandan individuals⁴⁵, all of which point
736 to an effect of this variant on HbA1c via non-glycaemic pathways.

737

738 Lastly, our credible set analysis identified rs1799815 (PPA=0.993) as the likely causal variant at the
739 *INSR* locus associated with FI. rs1799815 is a synonymous variant (Tyr3033Tyr) within *INSR*, the well-
740 known insulin receptor gene that regulates the insulin signalling pathway. *INSR* as a target gene for
741 this locus is further supported by our finding that rs1799815 colocalizes as an eQTL for *INSR*
742 expression in adipose tissue (details shown below). The remaining locus-trait associations with a
743 single variant in the 99% CS (**Supplementary Table 14**) point to variants that could be prioritised for
744 downstream functional follow-up to further elucidate their impact on glycaemic trait physiology.

745

746 In addition to identifying 99% CS with a single variant, trans-ancestry fine-mapping identified 99% CS
747 with 50 or fewer variants at 156 locus-trait associations (**Figure 4B, Supplementary Table 14**).

748 Overall, 74 locus-trait associations contained 87 variants with PPA>0.90; that is, some locus-trait
749 associations contain more than one variant with a high predicted probability of being causal as there
750 can be more than one causal variant in a locus (**Supplementary Table 15**). In addition to those
751 already described above, the identified variants are strong candidate causal variants that merit
752 prioritisation for future functional validation. For example, among the 87 variants, 10 are coding
753 variants including several missense such as the *HBB* Glu7Val mentioned above, *GCKR* Leu446Pro,
754 *RREB1* Asp1771Asn, *G6PC2* Pro324Ser, *GLP1R* Ala316Thr, and *TMPRSS6* Val736Ala, each of which
755 have been proposed or shown to affect gene function^{12,46-50}. We also additionally identify *AMPD3*
756 Val311Leu (PPA=0.989) and *TMC6* Trp125Arg (PPA>0.999) variants associated with HbA1c which
757 were previously detected in an exome array analysis but had not been fine-mapped with certainty
758 due to the absence of backbone GWAS data³⁰. Our current fine-mapping data now suggest these
759 variants are likely to be causal and identify the cognate genes as the effector transcripts driving
760 these associations.

761

762 Finally, we evaluated the resolution obtained in the trans-ancestry versus single-ancestry fine-
763 mapping (**Methods, Supplementary Note**). To do this, we compared the number of variants in 99%
764 CS across 98 locus-trait associations which, as suggested by FINEMAP, had a single causal variant in
765 both trans-ancestry and single-ancestry analyses. Fine-mapping within and across ancestries was
766 conducted using the same set of variants. At 8 of 98 locus-trait associations single-ancestry fine-
767 mapping identified a single variant in the CS. In addition, at 72 of the 98 locus-trait associations, the
768 number of variants in the 99% CS was smaller in trans-ancestry fine-mapping than in single-ancestry
769 analyses (**Figure 4C**), which likely reflects the larger sample size and differences in LD structure,
770 EAFs, and effect sizes across diverse populations. To quantify the estimated improvement in fine-
771 mapping resolution attributable to the multi-ancestry GWAS, we then compared 99% CS sizes from
772 the trans-ancestry fine-mapping to single-ancestry-specific data emulating the same total sample
773 size by rescaling the standard errors (**Methods**). Of the 72 locus-trait associations with estimated
774 improved fine-mapping in trans-ancestry analysis, resolution at 38 (53%) was improved because of
775 the larger sample size in the trans-ancestry fine-mapping analysis (**Figure 4C**), and this estimated
776 improved resolution would likely have been obtained in a European-only fine-mapping effort with
777 equivalent sample size. However, at 34 (47%) loci, the inclusion of samples from multiple diverse

778 populations yielded estimated improved resolution. On average, ancestry differences led to a
779 reduction in the median number of variants in the 99% CS from 24 to 15 variants (37.5% median
780 reduction; **Figure 4C**), demonstrating the value of conducting fine-mapping across ancestries.

781

782 **HbA1c Signal Classification**

783 We, and others, have previously suggested that HbA1c-associated variants appear to exert their
784 effects on HbA1c levels through both glycaemic and non-glycaemic pathways^{7,51}. Classification of
785 loci into these pathways can have important implications for T2D diagnostic accuracy^{7,52}. To further
786 elucidate the biology of HbA1c-associated variants, we took advantage of prior association results
787 for other glycaemic, RBC, and iron traits, and used a fuzzy clustering approach to classify variants
788 into their most likely mode of action (**Methods, Supplementary note**). Of the **218** HbA1c-associated
789 trans-ancestry lead variants and single-ancestry index variants, **27 (12%)** could not be characterized
790 due to missing summary statistics in the other datasets and **23 (11%)** could not be classified into a
791 “known” class (**Supplementary note**). The remaining signals were classified as principally: a)
792 glycaemic (**n=53; 24%**), b) affecting iron levels/metabolism (**n=12; 6%**), or c) RBC traits (**n=103; 47%**).
793 We found a genetic risk score (GRS) composed of all HbA1c-associated signals was strongly
794 associated with T2D risk (**OR=2.4, 95% CI 2.3-2.5, $P=2.4 \times 10^{-298}$**). However, when we tested
795 partitioned GRSs composed of these different classes of variants (**Methods**), we found the T2D
796 association was mainly driven by those variants influencing HbA1c through glycaemic pathways
797 (**OR=2.6, 95% CI 2.5-2.8, $P=1.1 \times 10^{-250}$**), with weaker evidence of association (despite the larger
798 number of variants in the GRS) and a more modest risk (**OR=1.4, 95% CI 1.2-1.7, $P=4.7 \times 10^{-4}$**)
799 imparted by signals in the mature RBC cluster that were not glycaemic (i.e. where those specific
800 variants had $P > 0.05$ for FI, 2hGlu and FG) (**Supplementary Figure 15, Supplementary note**). This
801 contrasts our previous finding where we found no significant association between a risk score of
802 non-glycaemic variants and T2D⁷. Our current results could be partly driven by T2D cases being
803 diagnosed based on HbA1c levels that may be influenced by the non-glycaemic signals, or by
804 glycaemic effects not captured by FI, 2hGlu or FG measures.

805

806 **Biological signatures of glycaemic trait associated loci**

807 To better understand distinct and shared biological signatures underlying variant-trait associations,
808 we conducted genomic feature enrichment, eQTL co-localisation, and tissue and gene-set
809 enrichment analyses across all four traits.

810

811 **Epigenomic landscape of trait-associated variants**

812 We next explored the genomic context underlying glycaemic trait loci by computing overlap
813 enrichment for static annotations such as coding, conserved regions, histone modification ChIP-seq
814 peaks, and super enhancers, merged across various cell types⁵³⁻⁵⁵ using the GREGOR tool⁵⁶. We
815 observed that FG, FI and HbA1c signals (**Supplementary Table 8**) were significantly ($P < 8.4 \times 10^{-4}$,
816 Bonferroni threshold correcting for 59 total annotations) enriched in evolutionarily conserved
817 regions, whereas 2hGlu signals were only nominally enriched (**Fig 5A, Supplementary Figure 16,**
818 **Supplementary Table 16**).

819

820 We then focussed on the epigenomic landscapes defined in individual cell/tissue types. Previously,
821 stretch enhancers (enhancer chromatin states ≥ 3 kb in length) in pancreatic islets were shown to be
822 highly cell-specific and strongly enriched with T2D risk signals⁵⁷. We therefore calculated the
823 enrichment of glycaemic trait-associated signals (**Supplementary Table 8**) in previously defined
824 stretch enhancers³⁹ across a diverse panel of cell types and tissues most relevant to the traits of
825 interest: pancreatic islets, skeletal muscle, adipose, and liver (**Methods**). These analyses strongly

826 suggest that variants associated with these glycaemic traits influence the function of tissue specific
827 enhancers. Namely, FG- and 2hGlu-associated signals have the highest enrichment in islet stretch
828 enhancers (FG: fold enrichment=4.70, $P=2.7\times 10^{-24}$; 2hGlu: fold enrichment=5.51, $P=3.6\times 10^{-4}$ **Figure**
829 **5A, Supplementary Table 17**), which highlights the relevance of pancreatic islet tissue for the
830 regulation of FG and 2hGlu. Interestingly, FI-associated variants are strongly enriched for overlap
831 with stretch enhancers in skeletal muscle (fold enrichment=3.17, $P=7.8\times 10^{-6}$) and adipose tissue (fold
832 enrichment=3.27, $P=1.8\times 10^{-7}$), which is consistent with these tissues being key targets of insulin
833 action and their involvement in the insulin resistance phenotype (**Figure 5A**). We note that the high
834 enrichment of stretch enhancers in individual cell types (see upper “stretch enhancer” labelled
835 portion of **Figure 5A**) as compared to super enhancers merged across cell types (see lower “static
836 annotations” labelled portion of **Figure 5A**) highlights the importance of using cell-specific
837 annotations in enrichment analyses. HbA1c-associated signals are enriched in stretch enhancers of
838 multiple cell types and tissues likely because of the complex nature of this trait, but have the
839 strongest enrichment in stretch enhancers from the blood-derived leukaemia cell line K562 (fold
840 enrichment=3.24, $P=1.21\times 10^{-7}$, **Figure 5A**). We next sought to identify potential cell specific
841 epigenomic enrichments that are associated with the classified HbA1c-associated variants
842 corresponding to the “hard” glycaemic and red blood cell clusters, the latter being the joint group of
843 mature red blood cell and reticulocyte clusters. We found that these partitioned variants display
844 expected cell type-specific enrichment trends with the HbA1c glycaemic variants significantly
845 enriched in islet stretch enhancers (fold enrichment=3.96, $P=3.69\times 10^{-16}$ **Figure 5B, Supplementary**
846 **Table 18**) and not in K562. Conversely, the HbA1c red blood cell variants are significantly enriched in
847 K562 stretch enhancers (fold enrichment=7.5, $P=2.08\times 10^{-14}$, **Figure 5B, Supplementary Table 18**) and
848 not in islets.

849
850 To complement the overlap enrichment results from GREGOR, we computed enrichment with two
851 additional approaches: fGWAS⁵⁸ and GARFIELD⁵⁹. These independent analyses yielded consistent
852 results (**Supplementary Figures 17-18, Supplementary Tables 16 and 19**), demonstrating
853 reproducibility across different approaches. **Notably, we also observed enrichment of FI-associated**
854 **variants in liver stretch enhancers (odds ratio=1.92, $P=1.7\times 10^{-4}$) when considering a more lenient**
855 **SNP significance threshold of $P<10^{-5}$ with the GARFIELD approach (Supplementary figure 18A). This**
856 **suggests that liver regulatory annotations are relevant for FI GWAS signals, but that we lack power**
857 **to detect significant enrichment using the genome-wide significant loci and the current set of**
858 **reference liver annotations.**

859
860 Given the observed enrichment of FI loci with stretch enhancers from adipose and skeletal muscle
861 tissue, we sought to explore these loci in more detail. We found that 11 of the 27 loci driving these
862 enrichment signals include variants that overlap stretch enhancers in both adipose and skeletal
863 muscle (**Figure 5C**). At the *COL4A2* locus, variants within an intronic region of the gene overlap
864 stretch enhancer chromatin states in adipose tissue, skeletal muscle, and a human skeletal muscle
865 myoblast (HSMM) cell line that are not shared across other cell types and tissues; among these
866 variants, rs9555695 (in the 99% CS) also overlaps accessible chromatin regions in adipose (**Figure**
867 **5D**). At a narrow signal (no proxy variants with LD $r^2>0.7$ in Europeans, for the lead trans-ancestry
868 rs62271373 variant), rs62271373 (PPA = 0.94) located in an intergenic region ~25kb from the
869 *LINC01214* gene overlaps stretch enhancer chromatin states in adipose and HSMM and active
870 enhancer chromatin states in skeletal muscle, but does not overlap any enhancer states in other
871 tissues (**Figure 5E**). The lead rs62271373 variant also overlaps an ATAC-seq peak in adipose tissue.
872 Collectively, the tissue-specific stretch enhancer epigenomic signatures at GWAS signals provide an
873 opportunity to nominate tissues where these variants are likely to be active. Such a map will be
874 helpful in future efforts to deconvolute GWAS signals into tissue-specific disease pathology.

875
876

877

878 Co-localisation of GWAS and eQTLs

879 Among the 99 novel glycaemic trait loci identified by this study, we identified co-localised eQTLs at
880 34 loci in blood, pancreatic islets, subcutaneous or visceral adipose, skeletal muscle, or liver,
881 providing suggestive evidence of causal genes (**Supplementary Table 20**). The co-localised eQTLs
882 include several genes previously reported at glycaemic trait loci: *ADCY5*, *CAMK1D*, *IRS1*, *JAZF1*, and
883 *KLF14*⁶⁰⁻⁶². For some additional loci, the co-localised genes have prior evidence for a role in
884 glycaemic regulation. For example, the lead trans-ancestry variant and likely causal variant,
885 rs1799815 (PPA=0.993, mentioned above), associated with FI is the strongest variant associated with
886 expression of *INSR*, encoding the insulin receptor, in subcutaneous adipose from METSIM ($P=2\times 10^{-9}$)
887 and GTEx ($P=5\times 10^{-6}$). The A allele at rs1799815 is associated with higher FI and lower expression of
888 *INSR*, which is consistent with the well-established relationship in humans and model organisms
889 between insulin resistance and reduced function of INSR protein⁶³. In a second example, rs841572,
890 the trans-ancestry lead variant associated with FG, is the variant with the highest PPA (PPA=0.535)
891 among the 20 variants in the 99% CS and is in strong LD ($r^2=0.87$) with the lead eQTL variant
892 (rs841576, also in the 99% CS) associated with expression of *SLC2A1* in blood from eQTLGen
893 ($P=1\times 10^{-8}$). *SLC2A1*, also known as *GLUT1*, encodes the major glucose transporter in brain, placenta,
894 and erythrocytes, and is responsible for glucose entry into the brain⁶⁴. The A allele at rs841572 is
895 associated with lower FG and lower *SLC2A1* expression. While rare missense variants in *SLC2A1* are
896 an established cause of seizures and epilepsy⁶⁵, our data suggest that *SLC2A1* variants also affect
897 plasma glucose levels within a healthy physiological range. **These novel associations and co-localised**
898 **eQTLs provide possible regulatory mechanisms for variant effects on genes to influence glycaemic**
899 **traits.**

900

901 The co-localised eQTLs also provide new insights into the mechanisms at glycaemic trait loci. For
902 example, rs9884482 (a variant in the 99% CS) is associated with FI and expression of *TET2* in
903 subcutaneous adipose ($P=2\times 10^{-20}$); rs9884482 is in high LD ($r^2=0.96$ in Europeans) with the lead *TET2*
904 eQTL variant (rs974801). *TET2* encodes a DNA-demethylase through which *TET2* can affect
905 transcriptional repression⁶⁶. Adipose Tet2 expression is reduced in diet-induced insulin resistance in
906 mice⁶⁷, and knockdown of Tet2 blocked adipogenesis by repressing *Pparg* expression^{67,68}.
907 Consistently, in human adipose tissue, rs9884482-C was associated with lower expression of *TET2*
908 and higher FI. In a second example, HbA1c-associated variant rs617948 (a variant in the 99% CS) is
909 the lead variant associated with expression of *C2CD2L* in blood from eQTLGen ($P=3\times 10^{-96}$). *C2CD2L*,
910 also known as *TMEM24*, has been shown to regulate pulsatile insulin secretion and facilitate release
911 of insulin pool reserves^{69,70}. The G allele at rs617948 was associated with higher HbA1c and lower
912 *C2CD2L*, providing evidence for a role of this insulin secretion protein in glucose homeostasis. Our
913 HbA1c “soft” clustering classification assigns this signal to both the “unknown” (0.51 probability) and
914 “reticulocyte” (0.42 probability) clusters, and this variant has no evidence for association with FG, FI
915 or 2hGlu ($P>0.05$), but is strongly associated with HbA1c ($P<6.8\times 10^{-8}$), reticulocytes (RET; $P<5\times 10^{-7}$)
916 and HbA1c adjusted for FG ($P<6.12\times 10^{-7}$; **Supplementary Table 21, Supplementary Note**). Together,
917 these results would suggest a possible effect of this variant on reticulocyte biology, and an effect on
918 insulin secretion (mediated through *C2CD2L*) which is not captured by any of our traits, both of
919 which potentially influencing HbA1c levels through different tissues, and providing a plausible
920 explanation for the classification as “unknown”.

921

922 Tissue Expression

923 Consistent with results based on effector transcripts and expression analysis based on GTEx data³⁰,
924 we found significant differences in tissue expression across the glycaemic trait-associated variants.
925 FG-associated variants were enriched for genes expressed in the pancreas (at FDR<0.05), while there
926 was insufficient power (insufficient number of genome-wide significant associations) in 2hGlu
927 analysis to identify enrichment for any tissues or cell types at a more relaxed FDR<0.2 threshold. FI-

928 associated variants were enriched for connective tissue and cells (which includes adipose tissue),
929 endocrine glands, blood cells, and muscles (at $FDR < 0.2$) and HbA1c-associated variants were
930 significantly enriched for genes expressed in the pancreas, hemic, and immune system (at $FDR < 0.05$)
931 (**Figure 6, Supplementary Table 22**). Consistent with our previous analysis³⁰, FI-enrichment for
932 connective tissue was driven by adipose tissue (subcutaneous and visceral), while the newly
933 described enrichment with endocrine glands was driven by the adrenal glands and cortex
934 (**Supplementary Table 22**). Beyond enrichment for genes expressed in glycaemic-related tissues, the
935 association of HbA1c-associated variants with genes expressed in blood is consistent with the role of
936 RBC in this glycaemic measure and our previous results³⁰.

937

938 The association between FI-associated variants (a surrogate for insulin resistance) and genes
939 expressed in adrenal glands is notable, suggesting a possible direct role for these genes in insulin
940 resistance. One hypothesis is that these genes might influence cortisol levels, which could
941 subsequently contribute to insulin resistance and FI levels through impairment of the insulin
942 receptor signalling pathway in peripheral tissues, as well as influencing body fat distribution,
943 stimulate lipolysis, and other indirect mechanisms^{71,72}.

944

945

946 Gene-set Analyses

947 Next, we performed gene-set analysis using DEPICT (**Methods**). In keeping with previous results³⁰,
948 we found distinct gene-sets enriched ($FDR < 0.05$) for each glycaemic trait (except 2hGlu, for which
949 genome-wide associations were insufficient to have power in this analysis). FG-associated variants
950 highlighted gene-sets involved in metabolism in addition to gene-sets involved in more general
951 cellular function such as “cytoplasmic vesicle membrane” and “circadian clock” (**Figure 7A**). In
952 contrast, in addition to metabolism related gene-sets FI-associated variants highlighted pathways
953 related to growth, cancer and reproduction (**Figure 7B**). This is consistent with the role of insulin as a
954 mitogenic hormone, and with epidemiological links between insulin and certain types of cancer⁷³
955 and reproductive disorders such as polycystic ovary syndrome⁷⁴. HbA1c-associated variants
956 highlighted a wide network of gene-sets (**Figure 7C**), including those linked to metabolism, as well as
957 those linked to haematopoiesis, again recapitulating our postulated effects of variants on glucose
958 and RBC biology. Additional pathways highlighted from HbA1c-associated variants also highlighted
959 previous “CREBP PPI” and lipid biology related to T2D⁷⁵ and HbA1c⁷⁶, respectively, and potential
960 new biology through which variants may influence HbA1c.

961

962 Discussion

963 Here we describe a large meta-analysis of GWAS of glycaemic traits for which 30% of the population
964 was composed of East Asian, Hispanic, African-American, South Asian and sub-Saharan African
965 participants, in addition to the European ancestry participants. Overall, this effort identified 242 loci
966 (235 trans-ancestry and seven single-ancestry), which jointly explain between 0.7% (2hGlu in
967 European ancestry individuals, $SE = 0.85\%$ for 2hGlu) and 6% (HbA1c in African American ancestry,
968 $SE = 1.2\%$ for HbA1c) of the variance in glycaemic traits in any given ancestry. Of these 242 glycaemic
969 trait loci, 114 have strong evidence of association with T2D ($P < 10^{-4}$; 83 loci with $P < 5 \times 10^{-8}$,
970 **Supplementary table 4**). Absence of strong evidence of association at the remaining loci (i.e. $P \geq 10^{-4}$)
971 suggests that for alleles more frequent than 5% we can exclude T2D $ORs \geq 1.07$ with 80% power
972 ($\alpha = 5 \times 10^{-8}$; and $ORs \geq 1.05$ for $\alpha = 10^{-4}$) given the current largest study which includes 228,499
973 T2D cases and 1,178,783 controls.²⁷ In total, we identified 486 signals associated with glycaemic
974 traits (including all trans-ancestry and single-ancestry lead and index variants, **Supplementary table**
975 **2**). Of these 486 signals, eight have $MAF < 1\%$, and 45 have $1\% \leq MAF < 5\%$ in all ancestries,
976 highlighting that 89% of signals identified are common in at least one of the ancestries studied.

977

978 A key aim of our study was to evaluate the added advantage of including population diversity into
979 genetic discovery and fine-mapping efforts. Beyond the overall larger sample size included in the
980 trans-ancestry meta-analysis, we were able to estimate the contribution of non-European ancestry
981 data in locus discovery and fine-mapping resolution. We found that 24 of the 99 newly discovered
982 loci owe their discovery to the inclusion of East Asian, Hispanic, African-American, South Asian and
983 sub-Saharan African participant data, due to differences in EAF and effect sizes across ancestries.
984

985 Comparison of 295 trans-ancestry lead variants (315 locus-trait associations) across ancestries
986 demonstrated that between 81.5% (for HbA1c) and 85.7% (for FG) of the trans-ancestry lead
987 variants had no evidence of trans-ancestry heterogeneity in allelic effects ($P>0.05$). Expanded
988 analyses including variants across the whole genome, demonstrated at least nominal concordance in
989 the direction of effects between populations of European ancestry and other ancestries for all but
990 the least significant association signals observed in European ancestry GWAS. These observations
991 are consistent with a tail of variants with modest but homogenous effects on glycaemic traits across
992 ancestries that would be amenable to discovery with even larger sample sizes in trans-ancestry
993 meta-analysis.
994

995 Given sample size and power limitations, genome-wide significant trait associated variants in a
996 single-ancestry (single-ancestry lead and index variants) explain only a modest proportion of trait
997 variance in that ancestry (**Figure 2**). We demonstrate that trans-ancestry meta-GWAS identified loci
998 (TA lead variants) provide additional information regarding trait variance explained above and
999 beyond that contributed by the ancestry-specific meta-analysis results (**Figure 2**). This shows that
1000 even though not all TA lead variants are genome-wide significant in all ancestries they contribute to
1001 the genetic architecture of the trait in most ancestries.
1002

1003 We evaluated for the first time the transferability of European ancestry-derived glycaemic trait PGS
1004 into other ancestries. In agreement with results for other traits^{36,77,78}, we confirm that European
1005 ancestry-derived PGS perform much worse when the test dataset is from a different ancestry. We
1006 note that each trait-specific PGS improves trait variance explained by between 3.5-fold (HbA1c) and
1007 6-fold (FG) in the European dataset (**Figure 3, Supplementary Table 12**) compared to using a score
1008 built only from TA lead variants and European index variants (**Figure 2, Supplementary tables 9-12**).
1009

1010 Despite development of novel approaches and software to derive polygenic risk scores⁷⁹, we note
1011 the difficulty in using summary level data to build a PGS in one ancestry and then apply it in test
1012 datasets of different ancestry. While PRS-CSauto³⁴ is able to use summary level data we noted that
1013 revision of the effect size estimates to account for LD required the use of reference panels that
1014 matched the ancestry of the test dataset. However, as the current version of the software lacks
1015 appropriate reference panels for many ancestries this precludes its broad application.
1016

1017 We further demonstrate that fine-mapping resolution is improved in trans-ancestry, compared to
1018 single-ancestry fine-mapping efforts. In ~50% of our loci, we were able to demonstrate the
1019 improvement is due to differences in EAF, effect size, or LD structure between ancestries, and not
1020 just due to the overall increased sample size available for trans-ancestry fine-mapping. By
1021 performing trans-ancestry fine-mapping, and co-localising GWAS signals with eQTL signals and
1022 coding variants, we identify new candidate causal genes. Altogether, these results provide additional
1023 strong motivation for continued expansion of genetic and genomic efforts in diverse populations,
1024 not least to improve understanding of these traits in diverse ancestries in whom individuals are
1025 often disproportionately affected by T2D.
1026

1027 Given data on four different glycaemic traits, and their utility to diagnose and monitor T2D and
1028 metabolic health, we also sought to characterise biological features underlying these traits. We

1029 show that despite significant sharing of genetic loci across the four glycaemic traits, each trait is also
1030 characterised by a unique set of features based on stretch enhancer, gene expression and gene-set
1031 signatures. Combining genetic data from these traits with T2D data will further elucidate pathways
1032 driving normal physiology and pathophysiology, and help further develop useful predictive scores for
1033 disease classification and management ^{4,5}.

1034

1035 **Online Methods**

1036 **Study design and participants**

1037 This study included trait data from four glycaemic traits: fasting glucose (FG), fasting insulin (FI), 2hr
1038 post-challenge glucose (2hGlu), and glycated haemoglobin (HbA1c). The total number of
1039 contributing cohorts ranged from 41 (2hGlu) to 131 (FG), and the maximum sample size for each
1040 trait ranged from 85,916 (2hGlu) to 281,416 (FG) (**Supplementary Table 1**). Overall, European
1041 ancestry (EUR) participants dominated the sample size for all traits, representing between 68.0%
1042 (HbA1c) to 73.8% (2hGlu) of the overall sample size. African Americans (AA) represented between
1043 1.7% (2hGlu) to 5.9% (FG) of participants; individuals of Hispanic ancestry (HISP) represented
1044 between 6.8% (FG) to 14.6% (2hGlu) of participants; individuals of East-Asian ancestry (EAS)
1045 represented between 9.9% (2hGlu) to 15.4% (HbA1c) of participants; and South-Asian ancestry (SAS)
1046 individuals represented between 0% (no contribution to 2hGlu) to 4.4% (HbA1c) of participants.
1047 Data from Ugandan participants were only available for the HbA1c analysis and represented 2% of
1048 participants.

1049

1050 **Phenotypes**

1051 Analyses included data for FG and 2hGlu measured in mmol/l, FI measured in pmol/l, and HbA1c in
1052 % [where possible, studies reported HbA1c as a National Glycohemoglobin Standardization Program
1053 (NGSP) percent]. Similar to previous MAGIC efforts ⁷, individuals were excluded if they had type 1 or
1054 type 2 diabetes (defined by physician diagnosis); reported use of diabetes-relevant medication(s); or
1055 had a FG ≥ 7 mmol/L, 2hGlu ≥ 11.1 mmol/L, or HbA1c $\geq 6.5\%$, as detailed in **Supplementary Table 1**.
1056 2hGlu measures were obtained 120 minutes after a glucose challenge in an oral glucose tolerance
1057 test (OGTT). Measures for FG and FI taken from whole blood were corrected to plasma level using
1058 the correction factor 1.13 ⁸⁰.

1059

1060 **Genotyping, quality control, and imputation**

1061 Each participating cohort performed study-level quality control, imputation, and association
1062 analyses following a shared analysis plan. Cohorts were genotyped using commercially available
1063 genome-wide arrays or the Illumina CardioMetaboChip (MetaboChip) array (**Supplementary Table 1**)
1064 ⁸¹. Prior to imputation, each cohort performed stringent sample and variant quality control (QC) to
1065 ensure only high-quality variants were kept in the genotype scaffold for imputation. Sample quality
1066 control checks included removing samples with low call rate $< 95\%$, extreme heterozygosity, sex
1067 mismatch with X chromosome variants, duplicates, first- or second-degree relatives (unless by
1068 design), or ancestry outliers. Following sample QC, cohorts applied variant QC thresholds for call rate
1069 ($< 95\%$), Hardy-Weinberg Equilibrium (HWE) $P < 1 \times 10^{-6}$, and minor allele frequency (MAF). Full
1070 details of QC thresholds and exclusions by participating cohort are available in **Supplementary Table**
1071 **1**.

1072

1073 Imputation was performed up to the 1000 Genomes Project phase 1 (v3) cosmopolitan reference
1074 panel ⁸², with a small number of cohorts imputing up to the 1000 Genomes phase 3 panel ¹⁹ or
1075 population-specific reference panels (**Supplementary Table 1**).

1076

1077 **Study level association analyses**

1078 Each of the glycaemic traits (FG, natural log FI, and 2hGlu) were regressed on BMI (except HbA1c),
1079 study-specific covariates, and principal components (unless implementing a linear mixed model).

1080 Analyses for FG, FI, and 2hGlu were adjusted for BMI as we had previously shown this did not
1081 materially affect results for FG and 2hGlu but improved our ability to detect FI-associated loci¹⁵. For
1082 simplicity, we refer to the traits as FG, FI and 2hGlu. For a discussion on collider bias see
1083 **Supplementary Note section 2c**. Both the raw and rank-based inverse normal transformed residuals
1084 from the regression were tested for association with genetic variants using SNPTTEST²³ or Mach2Qtl
1085^{83,84}. Poorly imputed variants, defined as imputation $r^2 < 0.4$ or INFO score < 0.4 , were excluded from
1086 downstream analyses (**Supplementary Table 1**). Following study level QC, approximately 12,229,036
1087 variants (GWAS cohorts) and 1,999,204 variants (Metabochip cohorts) were available for analysis
1088 (**Supplementary Table 1**).

1089

1090 **Centralised quality control**

1091 Each contributing cohort shared their summary statistic results with the central analysis group who
1092 performed additional QC using EasyQC⁸⁵. Allele frequency estimates were compared to estimates
1093 from 1000Gp1 reference panel⁸², and variants were excluded from downstream analyses if there
1094 was a minor allele frequency difference > 0.2 for AA, EUR, HISP, and EAS populations against AFR,
1095 EUR, MXL, and ASN populations from 1000 Genomes Phase 1, respectively, or a minor allele
1096 frequency difference > 0.4 for SAS against EUR populations. At this stage, additional variants were
1097 excluded from each cohort file if they met one of the following criteria: were tri-allelic; had a minor
1098 allele count (MAC) < 3 ; demonstrated a standard error of the effect size ≥ 10 ; or were missing an
1099 effect estimate, standard error, or imputation quality. All data that survived QC (approximately
1100 12,186,053 variants from GWAS cohorts and 1,998,657 variants from Metabochip cohorts) were
1101 available for downstream meta-analyses.

1102

1103 **Single-ancestry meta-analyses**

1104 Single-ancestry meta-analyses were performed within each ancestry group using the fixed-effects
1105 inverse variance meta-analysis implemented in METAL²⁰. We applied a double-genomic control (GC)
1106 correction^{15,86} to both the study-specific GWAS results and the single-ancestry meta-analysis results.
1107 Study-specific Metabochip results were GC-corrected using 4,973 SNPs included on the Metabochip
1108 array for replication of associations with QT-interval, a phenotype not correlated with our glycaemic
1109 traits¹⁵.

1110

1111 **Identification of single-ancestry index variants**

1112 To identify distinct association index variants across each chromosome within each ancestry
1113 (**Glossary box**), we performed approximate conditional analyses implemented in GCTA²¹ using the --
1114 cojo-slc option (autosomes) and distance-based clumping (X chromosome). Linkage disequilibrium
1115 (LD) correlations for GCTA were estimated from a representative cohort from each ancestry: WGHS
1116 (EUR); CHNS (EAS); SINDI (SAS); BioMe (AA); SOL (HISP) and Uganda (for itself). The results from
1117 GCTA were comparable when using alternative cohorts for the LD reference. For any index variant
1118 with a QC flag which caused reason for concern, we performed manual inspection of forest plots to
1119 decide whether the signal was likely to be real (**Supplementary note**). Among 335 single-ancestry
1120 index variants across all traits, this manual inspection was done for 40 signals of which 32 passed
1121 and 8 failed after inspection. Thus, a total of 327 single-ancestry index variants passed and 8 failed.

1122

1123 **Trans-ancestry meta-analyses**

1124 To leverage power across all ancestries, we also conducted trait-specific trans-ancestry meta-
1125 analysis by combining the single-ancestry meta-analysis results using MANTRA (**Supplementary**
1126 **Figure 3**)⁸⁷. We defined \log_{10} Bayes' Factor (BF) > 6 as genome-wide significant, approximately
1127 comparable to $P < 5 \times 10^{-8}$.

1128

1129 **Manual curation of trans-ancestry lead variants**

1130 To ensure trans-ancestry lead variants were robust, we performed manual inspection of forest plots
1131 by at least two authors, for any variants with flags indicating possible QC issues (**Supplementary**
1132 **Note**). Of 463 trans-ancestry lead variants across all traits, 184 passed without inspection, 131
1133 passed after inspection, and 148 failed after inspection.

1134

1135 ***Correlation in EAF and heterogeneity in effect sizes of TA lead variants across ancestries***

1136 For each pair of ancestries, we calculated Pearson's correlation in EAFs for each trans-ancestry lead
1137 variant. The pairwise summarised heterogeneity of effect sizes between ancestries was then tested
1138 using the joint F-test of heterogeneity³². The test statistic is the sum of Cochran Q-statistics for
1139 heterogeneity across all trans-ancestry signals. Under the null hypothesis, the statistics follows the χ^2
1140 distribution with n degrees of freedom, where n is the number of the trans-ancestry lead variants.

1141

1142 ***Concordance analyses of LD pruned European single-ancestry index variants into other ancestries***

1143 We compared the direction of effect of variants on each trait separately. For each trait, we identified
1144 variants reported in the European ancestry meta-analysis and each non-European ancestry meta-
1145 analysis, in turn. These variants were assigned to P-value bins, according to the strength of the
1146 association with the trait in the European ancestry meta-analysis: $P < 5 \times 10^{-8}$; $5 \times 10^{-8} \leq P < 5 \times 10^{-6}$; 5×10^{-6}
1147 $\leq P < 5 \times 10^{-4}$; $5 \times 10^{-4} \leq P < 0.05$; and $P \geq 0.05$. Within each P-value bin, we selected a set
1148 of "independent" variants that were separated by 1 Mb. We defined independence using a distance-
1149 based threshold because of differences in patterns of LD between ancestry groups. For each P-value
1150 bin, the proportion of variants with the same direction of effect on the trait between the two
1151 ancestries was calculated along with a P-value from the binomial test to determine if the proportion
1152 of variants with the same direction of effect was greater than that expected by chance (50%, one
1153 sided).

1154

1155 ***LD-pruned variant lists***

1156 Several downstream analyses (for example, genomic feature enrichment, genetic scores, and
1157 estimation of variance explained by associated variants) require independent LD-pruned variants (r^2
1158 < 0.1) to avoid double-counting variants which might otherwise be in LD with each other and that do
1159 not provide additional "independent" evidence. Therefore, for these analyses we generated
1160 different lists of either TA or single-ancestry LD pruned ($r^2 < 0.1$) variants, keeping in each case the
1161 variant with the strongest evidence of association (**Supplementary Table 8**). Subsequently, we
1162 combined TA and single-ancestry variant lists and conducted further LD pruning. For some analyses,
1163 we took the TA pruned variant list and added single-ancestry signals if the LD $r^2 < 0.1$, while for
1164 others we started with the single-ancestry pruned lists and supplemented with TA lead variants if
1165 the LD $r^2 < 0.1$. One exception was the list used for eQTL co-localisations, which included all single-
1166 ancestry European signals (without LD pruning) and supplemented with any additional TA lead
1167 variants (starting from the variants with the most significant P-values) in EUR LD $r^2 < 0.1$ with any of
1168 the variants already in list, and that reached at least $P < 1 \times 10^{-5}$ in the European ancestry meta-
1169 analysis.

1170

1171 **Trait variance explained by associated loci**

1172 To determine how much of the phenotypic variance of each trait could be explained by the
1173 corresponding trait-associated loci, variants were combined in a series of weighted genetic scores
1174 (GS). The analysis was performed in a subset of the cohorts included in the discovery GWAS (with
1175 representation from each ancestry) and in a smaller number of independent cohorts (European
1176 ancestry only). **Up to three different GS were derived per trait (and for each ancestry) in order to**
1177 **evaluate the potential for the trans-ancestry meta-GWAS identified loci to provide additional**
1178 **information above and beyond that contributed by the ancestry-specific meta-analysis results. These**
1179 **GS comprised: List A - single-ancestry signals; List B - single-ancestry signals plus trans-ancestry**
1180 **signals; and List C - trans-ancestry signals plus single-ancestry signals (Supplementary Table 8). In**

1181 the case of the European ancestry cohorts that contributed to the GWAS, we employed the method
1182 of Nolte *et al.*³³ to adjust the effect sizes (betas) from the GWAS for the contribution of that cohort,
1183 providing sets of cohort-specific effect sizes that were then used to generate the GS. The association
1184 between each GS and its corresponding trait was tested by linear regression and the adjusted R^2
1185 from the model extracted as an estimate of the variance explained.

1186
1187

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

1188 We used the PRS-CSauto³⁴ software to first build European ancestry-derived PGS for each glycaemic
1189 trait (FG, FI, 2hGlu, HbA1c) on the basis of summary statistics. However, PRS-CSauto does not
1190 perform well when the training dataset is relatively small and the genetic architecture is sparse.³⁴
1191 Consequently, 2hGlu was excluded from this analysis. For each trait, to obtain European ancestry
1192 training and test datasets, we first removed all cohorts only genotyped on the MetaboChip which
1193 were not included in this analysis. From the remaining cohorts we then removed five of the largest
1194 European cohorts contributing to the respective European ancestry meta-analysis. For each trait,
1195 these five cohorts were meta-analysed and used as the European ancestry test dataset.
1196 Subsequently, the remaining European ancestry cohorts were also meta-analysed and used as the
1197 European ancestry training dataset. For each of the other ancestries, cohorts only genotyped on the
1198 MetaboChip were also removed, and the remaining cohorts were meta-analysed, and used as the
1199 non-European ancestry test datasets. Variants with $MAF < 0.05$ or missing in over half of the
1200 individuals in the training dataset were removed.^{34,88} The PGS for each trait was built using PRS-
1201 CSauto with default settings³⁴ with the effect size estimates based on the European training dataset
1202 being revised based on an LD reference panel matching the test dataset. The proportion of the trait
1203 variance explained by the European ancestry-derived PGS (R^2) was estimated using the R package
1204 "gtx"⁸⁹ based on the revised effect sizes and summary statistics from the test dataset for each
1205 ancestry.
1206

1207
1208

Fine-mapping

1209 Of the 242 loci identified in this study, 237 were autosomal loci which we took forward for fine-
1210 mapping (**Supplementary Table 2**). We used the Bayesian fine-mapping method FINEMAP⁹⁰ (version
1211 1.1) to refine association signals and attempt to identify likely causal variants at each locus.
1212 FINEMAP estimates the maximum number of causal variants at each locus, calculates the posterior
1213 probability of each variant being causal, and proposes the most likely configuration of causal
1214 variants. The posterior probabilities of the configurations in each locus were used to construct 99%
1215 credible sets.
1216

1217

1218 We performed both single-ancestry and trans-ancestry fine-mapping. In both analyses, only data
1219 from cohorts genotyped on GWAS arrays were used, and analyses were limited to trans-ancestry
1220 lead variants and other single-ancestry lead variants present in at least 90% of the samples for each
1221 trait. For the single-ancestry fine-mapping, FINEMAP estimates the number of causal variants in a
1222 region up to a maximum number, which we set to be two plus the number of distinct signals
1223 identified from the GCTA signal selection. FINEMAP uses single-ancestry and trait-specific z-scores
1224 from the fixed-effect meta-analysis in METAL²⁰ and an ancestry-specific LD reference, which we
1225 created from a subset of cohorts (combined sample size > 30% of the sample size for that ancestry),
1226 weighting each cohort by sample size. In the trans-ancestry fine-mapping, FINEMAP was similarly
1227 used to estimate the number of causal variants starting with two, and trait-specific z-scores and LD
1228 maps were generated from the sample size weighted average of those used in the single-ancestry
1229 fine-mapping. The maximum number of causal variants was iteratively increased by one until it was
1230 larger than the number of causal variants supported by data (Bayes factor), which was the estimated
1231 maximum number of causal variants used in the final run of fine-mapping analysis.

1232
1233 To compare fine-mapping results obtained from the single-ancestry and trans-ancestry efforts,
1234 analyses were limited to fine-mapping regions with evidence for a single likely causal variant in both,
1235 enabling a straightforward comparison of credible sets (**Supplementary note**). To ensure any
1236 difference in the fine-mapping results was not driven by different sets of variants being present in
1237 the different analyses, we repeated the single-ancestry fine-mapping limited to the same set of
1238 variants used in the trans-ancestry fine-mapping. The fine-mapping resolution was assessed based
1239 on comparisons of the 99% credible sets in terms of number of variants included in the set, and
1240 length of the region. To assess whether the improvement in the trans-ancestry fine-mapping was
1241 due to differences in LD, increased sample size, or both, we repeated the trans-ancestry fine-
1242 mapping mimicking the sample size present in the single-ancestry fine-mapping by dividing the
1243 standard errors by the square root of the sample size ratio and compared the results with those
1244 from the single-ancestry fine-mapping.

1245 1246 **Functional Annotation of trait-associated variants**

1247 1248 ***HbA1c signal classification***

1249 There were 218 HbA1c-associated signals from either the single-ancestry (i.e. all GCTA-signals from
1250 any ancestry) or trans-ancestry meta-analyses. To classify these signals in terms of their likely mode
1251 of action (i.e., glycaemic, erythrocytic, or other⁷), we examined association summary statistics for
1252 the lead variants at the 218 signals in other large European datasets for 19 additional traits: three
1253 glycaemic traits from this study (FG, 2hGlu and FI); seven mature red blood cell (RBC) traits^{91,92} (red
1254 blood cell count, mean corpuscular volume, haematocrit, mean corpuscular haemoglobin, mean
1255 corpuscular haemoglobin concentration, haemoglobin concentration and red cell distribution
1256 width); five reticulocyte traits (reticulocyte count, reticulocyte fraction of red cells, immature
1257 fraction of reticulocytes, high light scatter reticulocyte count and high light scatter percentage of red
1258 cells)^{91,92}, and four iron traits (serum iron, transferrin, transferrin saturation and ferritin)⁹³. Of the
1259 218 HbA1c signals, data were available for the lead (n=183) or proxy (European LD $r^2 > 0.8$, n = 8)
1260 variants at 191 signals.

1261
1262 The additional traits were clustered using hierarchical clustering to ensure biologically related traits
1263 would cluster together (**Supplementary note**). We then used a non-negative matrix factorization
1264 (NMF)⁹⁴ process to cluster the HbA1c signals. Each cluster was labelled as glycaemic, reticulocyte,
1265 mature RBC, or iron related based on the strength of association of signals in the cluster to the
1266 glycaemic, reticulocyte, mature RBC and iron traits (**Supplementary note**). To verify that our cluster
1267 naming was correct, we used HbA1c association results conditioned on either FG or iron traits, or
1268 type 2 diabetes association results (**Supplementary note**).

1269 1270 ***HbA1c genetic risk scores (GRSs) and type 2 diabetes (T2D) risk***

1271 We constructed GRS for each cluster of HbA1c-associated signals (based on hard clustering) and
1272 tested the association of each cluster with T2D risk using samples from the UK Biobank. Pairs of
1273 HbA1c signals in LD (EUR $r^2 > 0.10$) were LD pruned by removing the signal with the less significant P -
1274 value of association with HbA1c. The GRS for each cluster was calculated based on the logarithm of
1275 odds ratios from the latest T2D study summary statistics⁹⁵ and UK Biobank genotypes imputed to
1276 the Haplotype Reference Consortium¹⁹. From 487,409 UK Biobank samples, we excluded
1277 participants for the following reasons: 373 with mismatched sex; 9 not used in the kinship
1278 calculation; 78,365 non-European ancestry individuals; and 138,504 with missing T2D status, age, or
1279 sex information. We further removed 26,896 related participants (kinship > 0.088 , preferentially
1280 removing individuals with the largest number of relatives and controls where a T2D case was related
1281 to a control). T2D cases were defined by: (i) a history of diabetes without metformin or insulin
1282 treatment, (ii) self-reported diagnosis of T2D, or (iii) diagnosis of T2D in a national registry (N =

1283 17,022). Controls were participants without a history of T2D (N = 226,240). We tested for association
1284 between each GRS and T2D using logistic regression including covariates for age, sex, and the first
1285 five principal components. Significance of association was evaluated by a bootstrap approach to
1286 incorporate the variance of each HbA1c associated signal in the T2D summary data. To do this, we
1287 generated the GRS of each cluster 200 times by resampling the logarithm of odds ratio of each signal
1288 with T2D. For each non-glycaemic class that had a GRS significantly associated with T2D, we
1289 performed sensitivity analyses to evaluate whether the association was driven from variants that
1290 also belonged to a glycaemic cluster when using a soft clustering approach (the signals were
1291 classified as also glycaemic in the soft clustering or had an association $P \leq 0.05$ with any of the three
1292 glycaemic traits).

1293

1294 **Chromatin states**

1295 To identify genetic variants within association signals that overlapped predicted chromatin states,
1296 we used a previously published, 13 chromatin state model that included 31 diverse tissues, including
1297 pancreatic islets, skeletal muscle, adipose, and liver³⁹. Briefly, this model was generated from
1298 cell/tissue ChIP-seq data for H3K27ac, H3K27me3, H3K36me3, H3K4me1, and H3K4me3, and input
1299 control from a diverse set of publicly available data^{53,57,96,97} using the ChromHMM program⁹⁸. As
1300 reported previously³⁹, stretch enhancers were defined as contiguous enhancer chromatin state
1301 (Active Enhancer 1 and 2, Genic Enhancer and Weak Enhancer) segments longer than 3kb⁵⁷.

1302 **Enrichment of genetic variants in genomic features**

1303 We used GREGOR (version 1.2.1) to calculate the enrichment of GWAS variants overlapping static
1304 and stretch enhancers⁵⁶. For calculating the enrichment of glycaemic trait-associated variants in
1305 these annotations, we used the filtered list of trait-associated variants as described above
1306 (**Supplementary Table 8**) as input. For calculating the enrichment of sub-classified HbA1c variants,
1307 we included the list of loci characterized as Glycaemic, another list of loci characterized as
1308 Reticulocyte or mature Red Blood Cell, collectively representing the red blood cell fraction, along
1309 with lists of iron related or unclassified loci (**Supplementary Table 18**). We used the following
1310 parameters in GREGOR enrichment analyses: European r^2 threshold (for inclusion of variants in LD
1311 with the lead variant) = 0.8, LD window size = 1 Mb, and minimum neighbour number = 500.

1312

1313 We used fGWAS (version 0.3.6)⁵⁸ to calculate enrichment of glycaemic trait-associated variants in
1314 static and stretch enhancer annotations using summary level GWAS results. We used the default
1315 fGWAS parameters for enrichment analyses for individual annotations for each trait. For each
1316 annotation, the model provided the natural log of maximum likelihood estimate of the enrichment
1317 parameter. Annotations were considered as significantly enriched if the log2 (parameter estimate)
1318 and respective 95% confidence intervals were above zero or significantly depleted if the log2
1319 (parameter estimate) and respective 95% confidence intervals were below zero.

1320

1321 We tested enrichment of trait-associated variants in static and stretch enhancer annotations with
1322 GARFIELD (v2)⁵⁹. We formatted annotation overlap files as required by the tool; prepared input data
1323 at two GWAS thresholds - of 1×10^{-5} and a more stringent 1×10^{-8} by pruning and clumping with default
1324 parameters (garfield-prep-chr script). We calculated enrichment in each individual annotation using
1325 garfield-test.R with $-c$ option set to 0. We also calculated the effective number of annotations using
1326 the garfield-Meff-Adj.R script. We used the effective number of annotations for each trait to obtain
1327 Bonferroni corrected significance thresholds for enrichment for each trait.

1328

1329 **eQTL analyses**

1330 To aid in the identification of candidate casual genes at the European-only and trans-ancestry
1331 association signals, we examined whether any of the lead variants associated with glycaemic traits
1332 (**Supplementary Table 8**) were also associated with expression level (FDR < 5%) of nearby transcripts
1333 located within 1 Mb in existing eQTL data sets of blood, subcutaneous adipose, visceral adipose,

1334 skeletal muscle, and pancreatic islet samples^{60,61,99-102}. LD was estimated from the collected cohort
1335 pairwise LD information, where available, else from the European samples in 1000G phase 3. GWAS
1336 and eQTL signals likely co-localise when the GWAS variant and the variant most strongly associated
1337 with the expression level of the corresponding transcript (eSNP) exhibit high pairwise LD ($r^2 > 0.8$;
1338 1000 Genomes Phase 3, EUR). At these signals, we conducted reciprocal conditional analyses to test
1339 association between the GWAS variant and transcript level when the eSNP was also included in the
1340 model, and vice versa. We report GWAS and eQTL signals as co-localised if the association for the
1341 eSNP was not significant (FDR $\geq 5\%$) when conditioned on the GWAS variant; we also report signals
1342 from the eQTLGen whole blood meta-analysis data that meet only the LD threshold because
1343 conditional analysis was not possible.

1344

1345 **Tissue and gene-set analysis**

1346 We performed enrichment analysis using DEPICT (Data-driven Expression-Prioritized Integration for
1347 Complex Traits) version 3, specifically developed for 1000 Genomes Project imputed meta-analysis
1348 data¹⁰³ to identify cell types and tissues in which genes at trait-associated variants were strongly
1349 expressed, and to detect enrichment of gene-sets or pathways. DEPICT data included human gene
1350 expression data for 19,987 genes in 10,968 reconstituted gene sets, and 209 tissues/cell types.
1351 Because gene expression data in DEPICT is based on European samples and LD, we selected trait-
1352 associated variants with $P < 10^{-5}$ in the European meta-analysis and tested for enrichment of signals
1353 in each reconstituted gene-set, and each tissue or cell type. Enrichment results with a false discovery
1354 rate (FDR) < 0.05 were considered significant. We ran DEPICT based on association results for all
1355 traits among: (i) cohorts with genome-wide data, or (ii) all cohorts (genome-wide and Metachip
1356 cohorts). Because results were broadly consistent between the two approaches, we present results
1357 from the analysis that contained all cohorts as it had greater statistical power.

1358

1359 **References**

1360

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1668

1669 **Competing interests statement**

1670 The authors declare the existence of a financial/non-financial competing interest. Full disclosures are
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1672

1676 **Figure Legends**

1678 **Figure 1 - Summary of all 242 loci identified in this study.** 235 trans-ancestry loci are shown in
1679 orange (novel) or black (established) along with seven single-ancestry loci (blue) represented by
1680 nearest gene. Each locus is mapped to corresponding chromosome (outer segment). Each set of
1681 rows shows the results from the trans-ancestry analysis (orange) and each of the ancestries:
1682 European (purple), African American (tan), East Asian (grey), South Asian (green), Hispanic (yellow),
1683 sub-Saharan African (Ugandan-pink). Loci with a corresponding type 2 diabetes signal are
1684 represented by red circles in the middle of the plot.

1685 **Figure 2 – Trait variance explained by associated loci.** The boxplots show the maximum, first
1686 quartile, median, third quartile and minimum of trait variance explained when using a genetic score
1687 with single-ancestry lead and index variants (EUR, AA, EAS, HISP and SAS) or a combination of
1688 individual trait trans-ancestry lead variants and single-ancestry lead and index variants (TA+EUR,
1689 TA+AA, TA+EAS, TA+HISP and TA+SAS). Variance explained for each trait (FG, FI and HbA1c) in each
1690 ancestry is shown on different panels and in different colours. R^2 was estimated in 1 to 11 cohorts
1691 with sample sizes ranging from 489 to 9,758 (**Supplementary Tables 9-12**).

1692 **Figure 3 – Transferability of PGS across ancestries.** For each trait, the barplots represent trait
1693 variance explained when using a European ancestry-derived PGS in European, East Asian and African
1694 American test datasets. Variance explained (the height of each bar) for each trait (FG, FI and HbA1c)
1695 in each ancestry is shown on different panels and in different colours.
1696

1697 **Figure 4 - Trans-ancestry fine-mapping.** A) Number of plausible causal variants at each locus-trait
1698 association derived from FINEMAP. B) Number of variants within each 99% credible set. Twenty-one
1699 locus-trait associations at 19 loci were mapped to a single variant in the 99% credible set. C) Fine-
1700 mapping resolution. For each of the 98 locus-trait associations with a predicted single causal variant
1701 in both trans-ancestry and single-ancestry analyses, the number of variants included in the 99%
1702 credible set in the single-ancestry fine-mapping (x axis; logarithmic scale) is plotted against those in
1703 the trans-ancestry fine-mapping (y axis; logarithmic scale). Trans-ancestry and single-ancestry fine-
1704 mapping were based on the same set of variants. After removing eight locus-trait associations with

1705 one variant in the 99% credible sets in both trans-ancestry and single-ancestry analyses, there were
1706 18 locus-trait associations (in grey) where trans-ancestry fine-mapping did not improve the
1707 resolution of fine-mapping results (i.e. number of variants in the 99% credible set did not decrease).
1708 Of the 72 locus-trait associations with improved trans-ancestry fine-mapping resolution (blue and
1709 red) further analyses in European fine-mapping emulating the total sample size in trans-ancestry
1710 fine-mapping demonstrated that 34 locus-trait associations (in red) were improved because of both
1711 total sample size and differences across ancestries, while 38 locus-trait associations (in blue) were
1712 only improved due to increased sample size in the original trans-ancestry fine-mapping analysis.

1713 **Figure 5 - Epigenomic landscape of trait-associated variants.** A: Enrichment of GWAS variants to
1714 overlap genomic regions including 'Static Annotations' which are common or 'static' across cell types
1715 and 'Stretch Enhancers' which are identified in each tissue/cell type. The numbers of signals for each
1716 trait are indicated in parentheses. Enrichment was calculated using GREGOR⁵⁶. Significance (red) is
1717 determined after Bonferroni correction to account for 59 total annotations tested for each trait;
1718 nominal significance ($P < 0.05$) is indicated in yellow. B: Enrichment for HbA1c GWAS signals
1719 partitioned into "hard" Glycaemic and Red Blood Cell cluster (signals from "hard" mature Red Blood
1720 Cell and reticulocyte clusters together) to overlap annotations including stretch enhancers in Islets
1721 and the blood-derived leukemia cell line K562, respectively (additional partitioned results in
1722 **Supplementary Table 18**). C: Individual FI GWAS signals that drive enrichment in Adipose and
1723 Skeletal Muscle stretch enhancers. D, E: Genome browser shots of FI GWAS signals – intronic region
1724 of the *COL4A2* gene (D) and an inter-genic region ~25kb from *LINC01214* gene (E) showing GWAS
1725 SNPs (lead and LD $r^2 > 0.8$ proxies), ATAC-seq signal tracks and chromatin state annotations in
1726 different tissues/cell types.

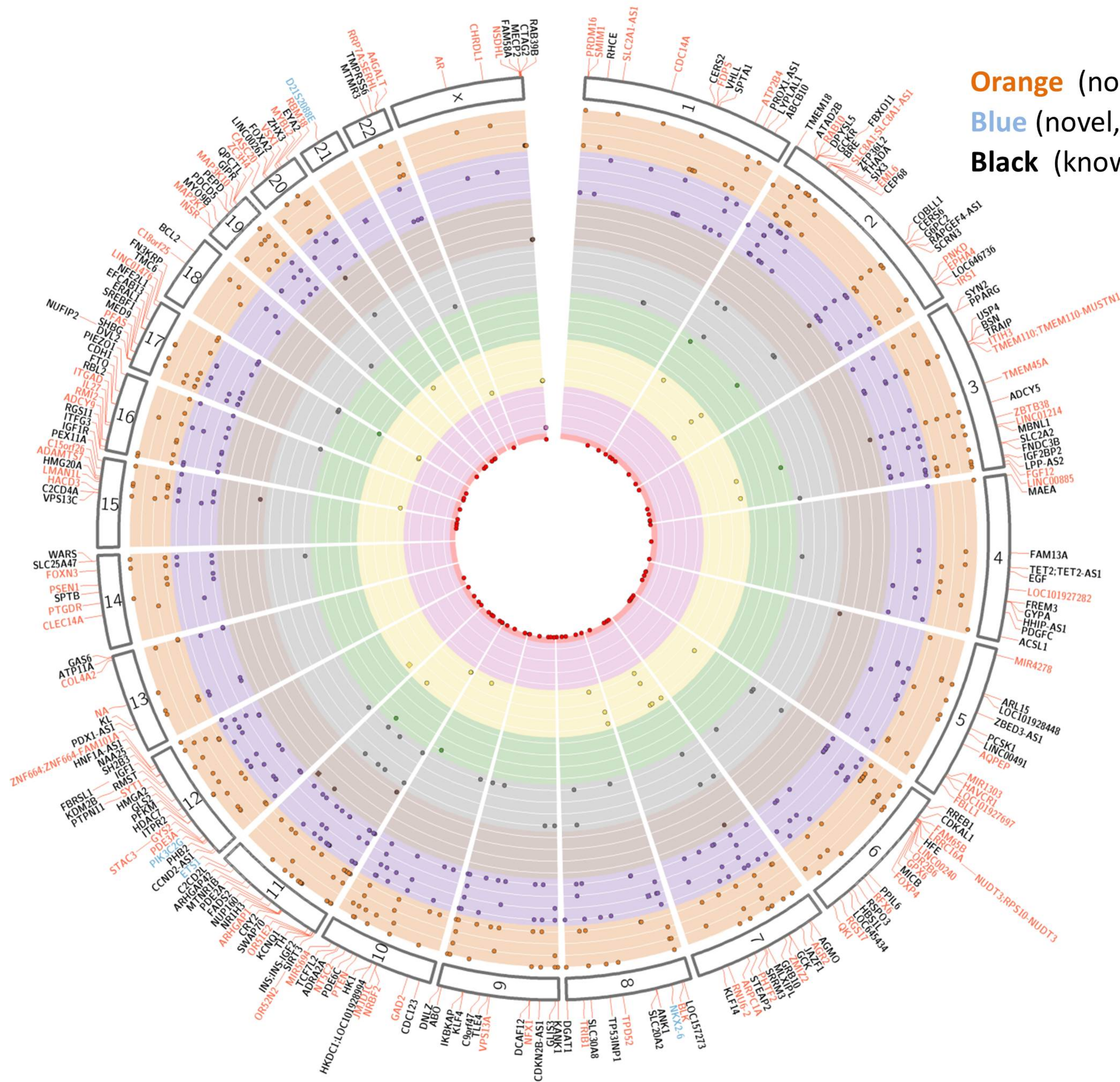
1727 **Figure 6 - Tissues and cell types significantly enriched for genes within glycaemic-associated loci.**
1728 Top panel FG-associated loci, middle panel FI-associated loci, bottom panel Hba1c-associated loci.
1729 FDR thresholds are shown in red ($q < 0.05$), orange ($q < 0.2$), grey ($q \geq 0.2$).

1730 **Figure 7 - Gene-set enrichment analyses.** Results from affinity-propagation clustering of significantly
1731 enriched gene sets ($FDR < 0.05$) identified by DEPICT for A) FG, B) FI, and C) HbA1c. Each node is a
1732 cluster of gene-sets represented by an exemplar gene-set with similarities between the clusters
1733 represented by the Pearson correlation coefficients ($r > 0.3$). The nodes are coloured according to the
1734 minimum gene-set enrichment p-value for gene-sets in that cluster. Example clusters are expanded
1735 to show the contributing gene-sets.

1736 **Tables**

1737

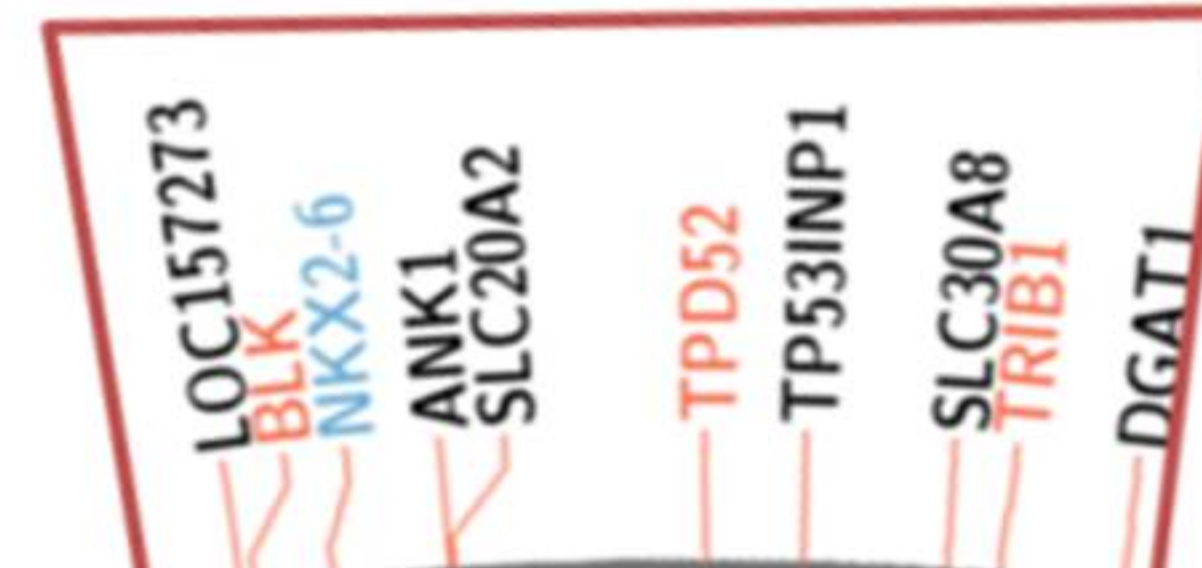
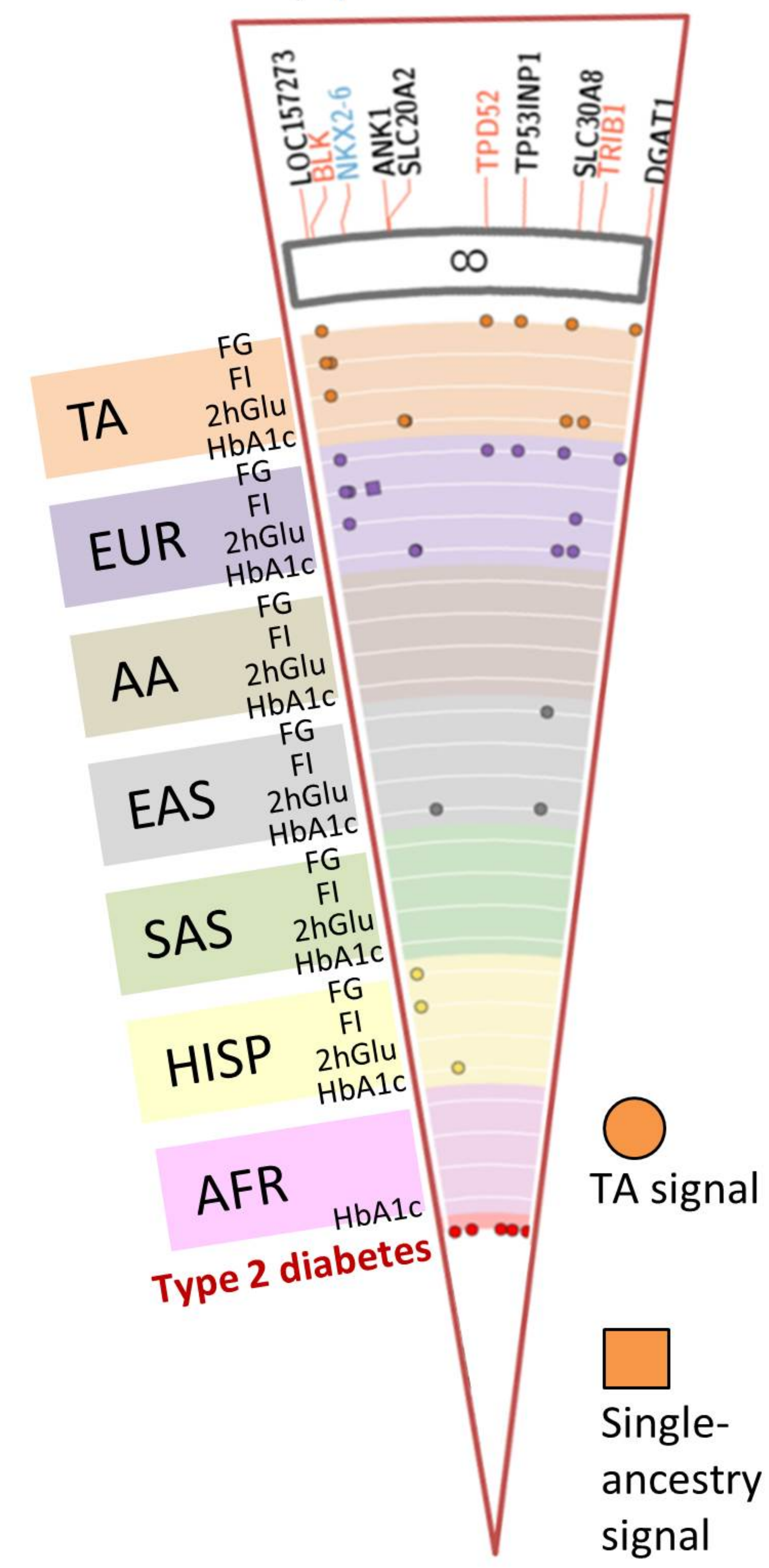
1738 **Table 1 – Glossary of terms**



Orange (novel)

Blue (novel, single-ancestry)

Black (known)



TA

EUR

AA

EAS

SAS

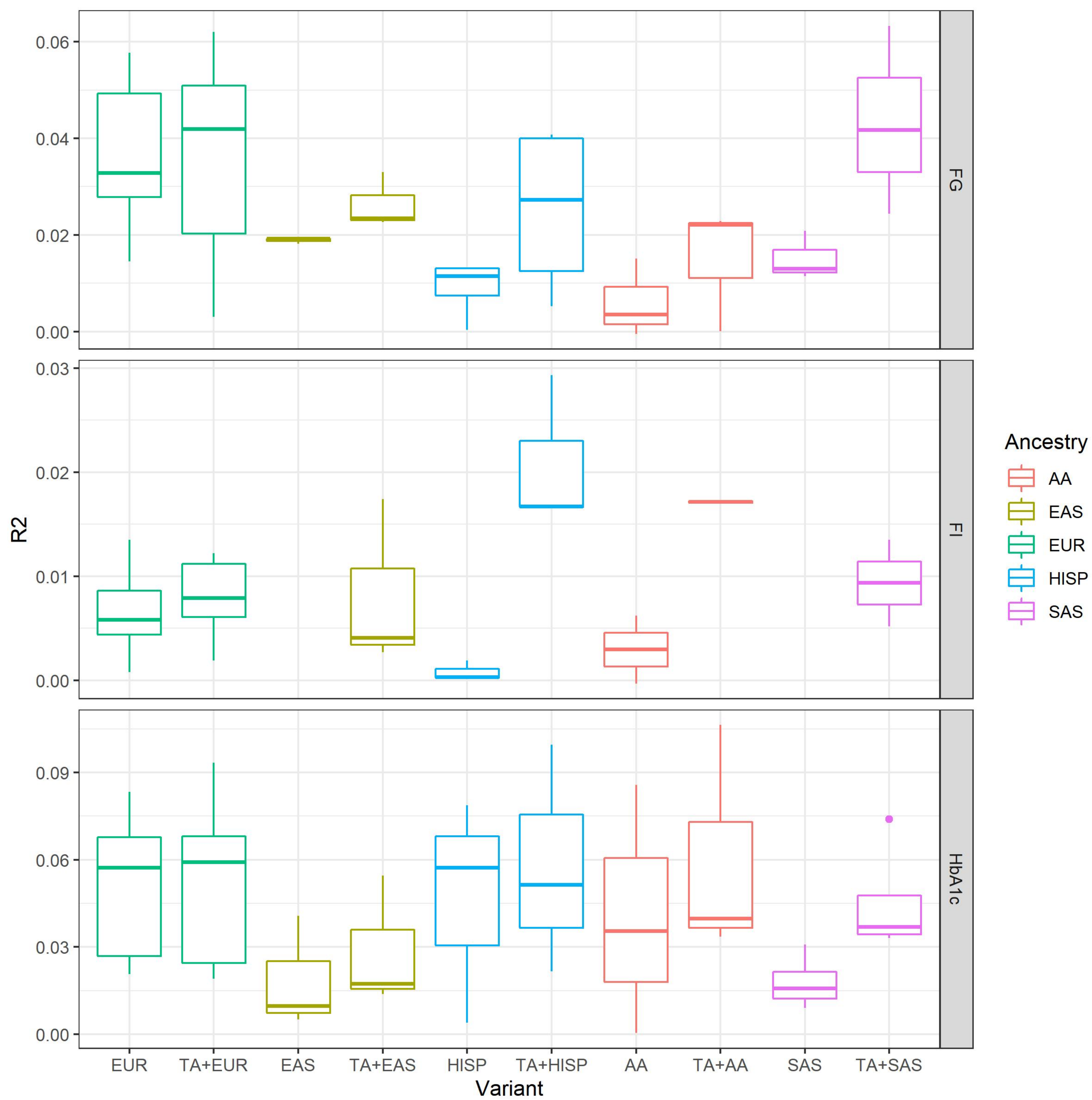
HISP

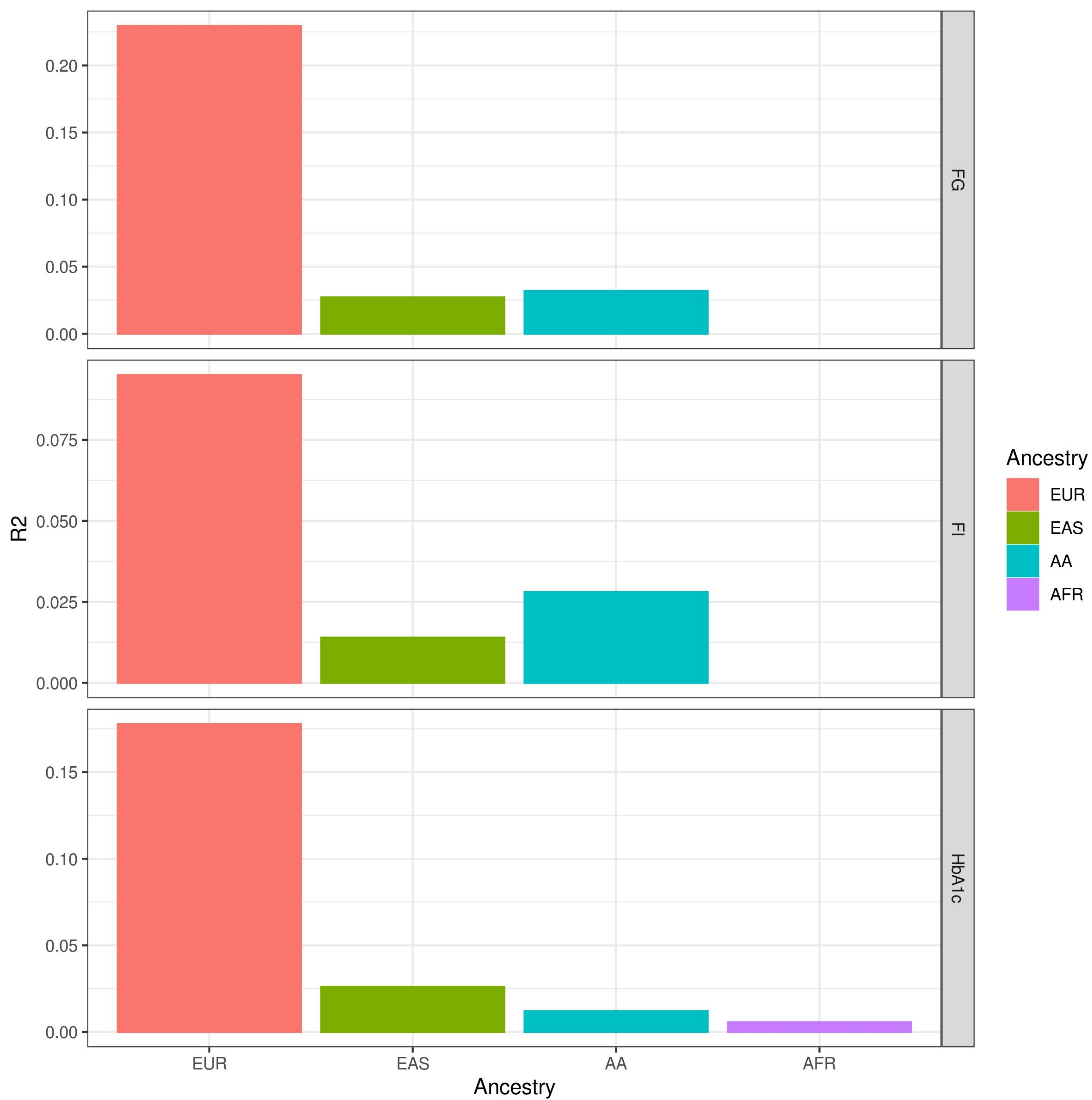
AFR

Type 2 diabetes

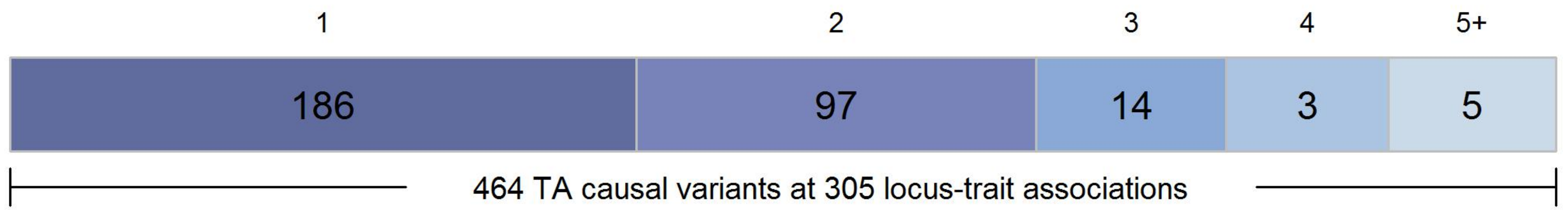
○ TA signal

□ Single-ancestry signal

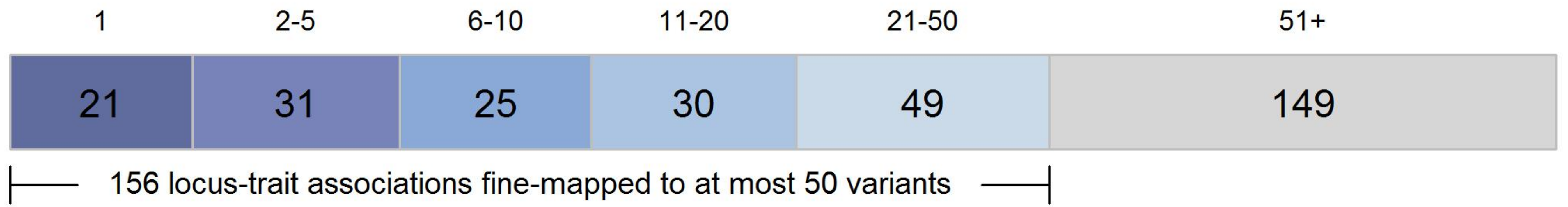




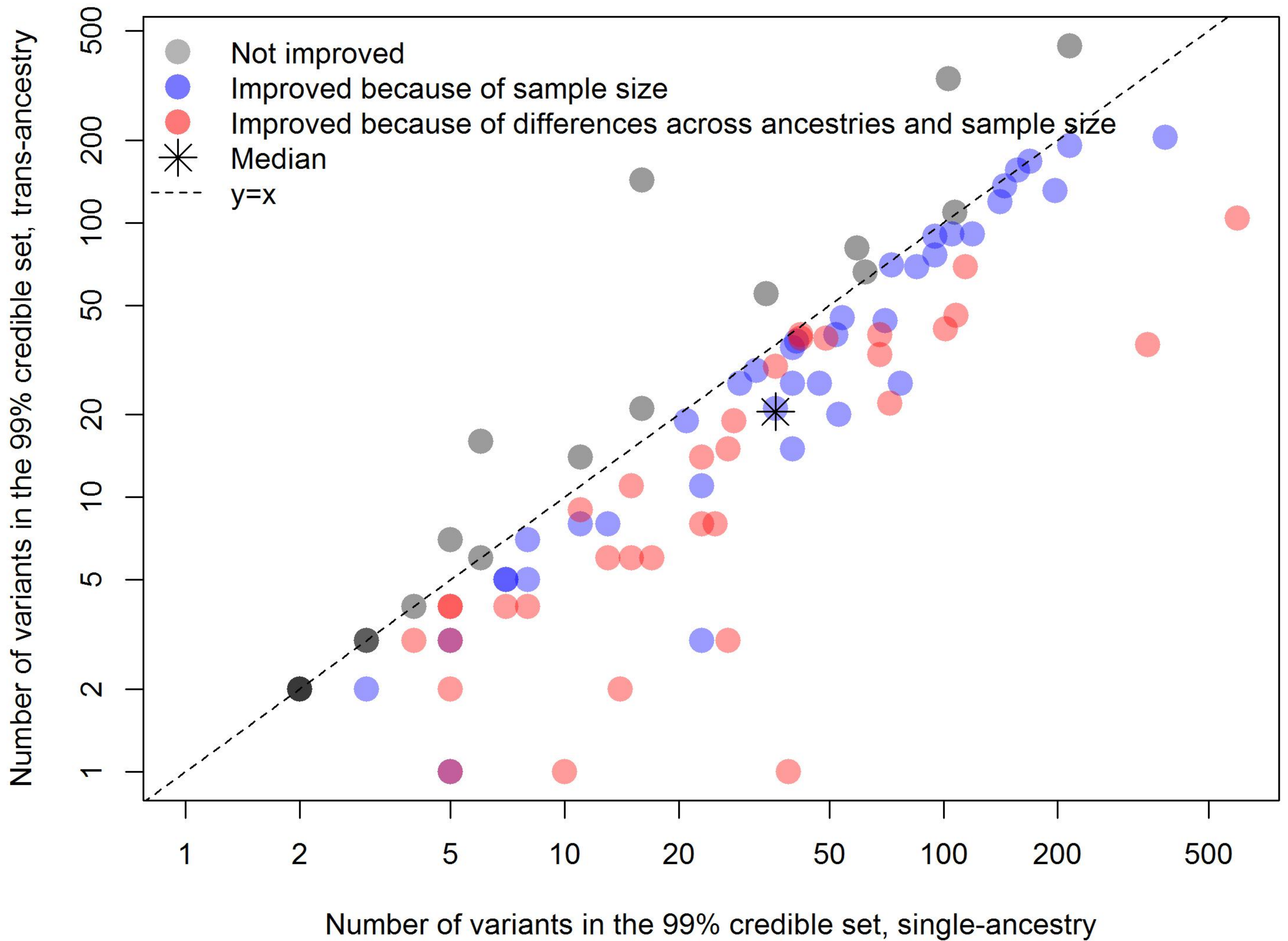
A. Estimated number of causal variants at each locus-trait association

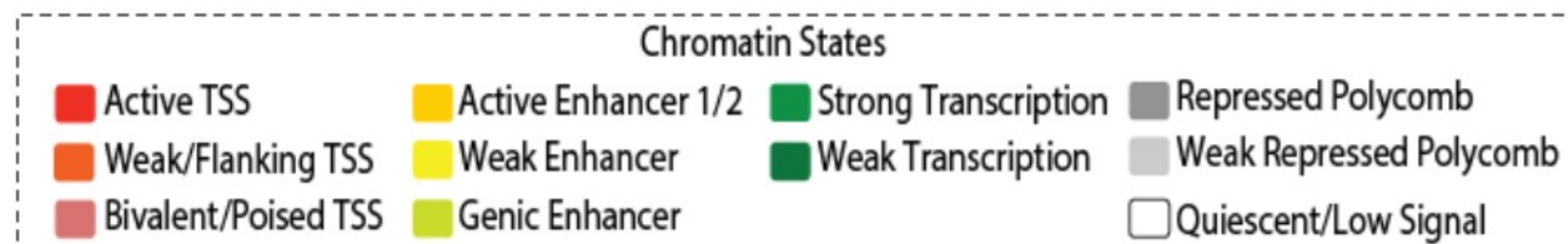
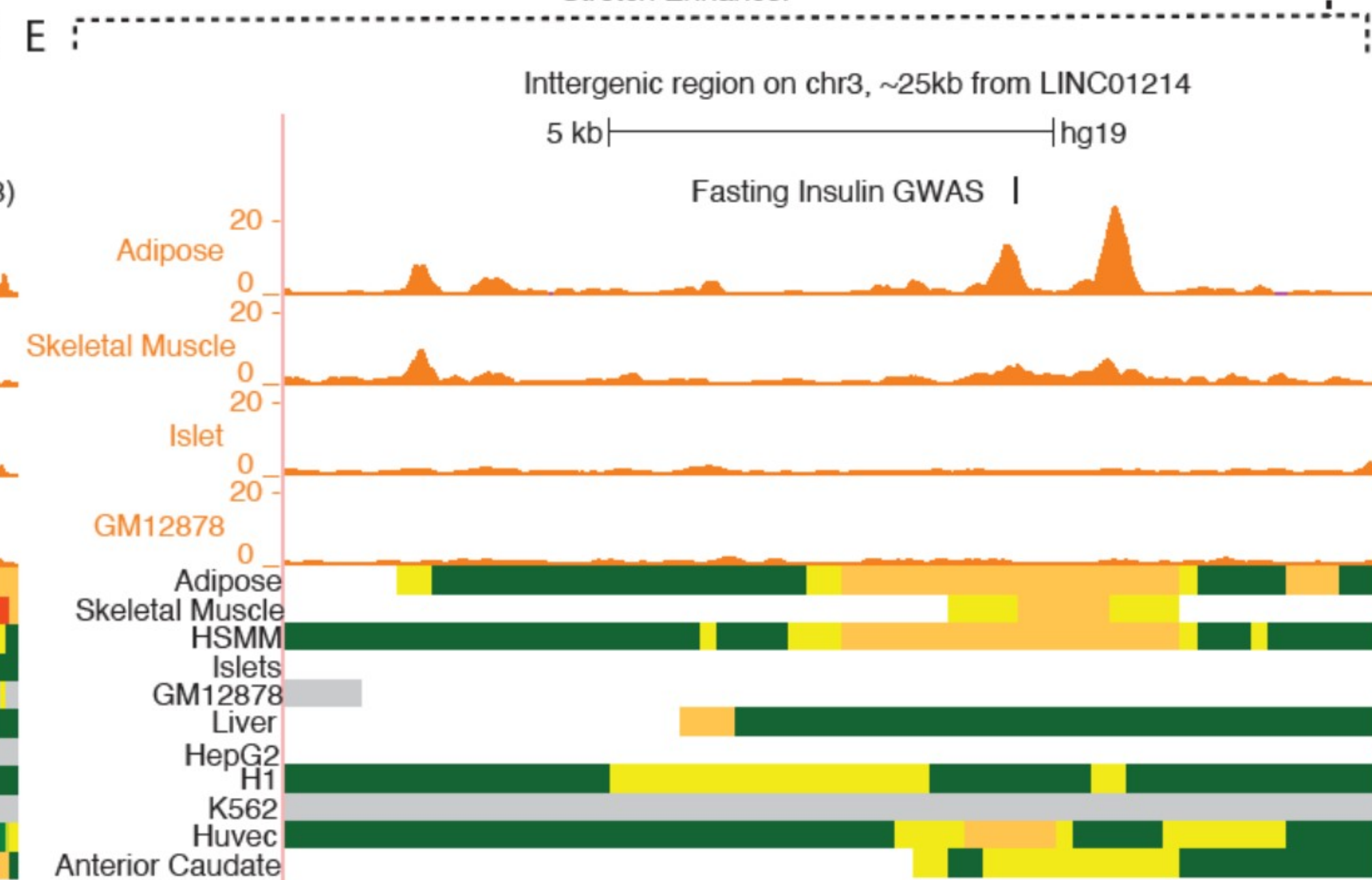
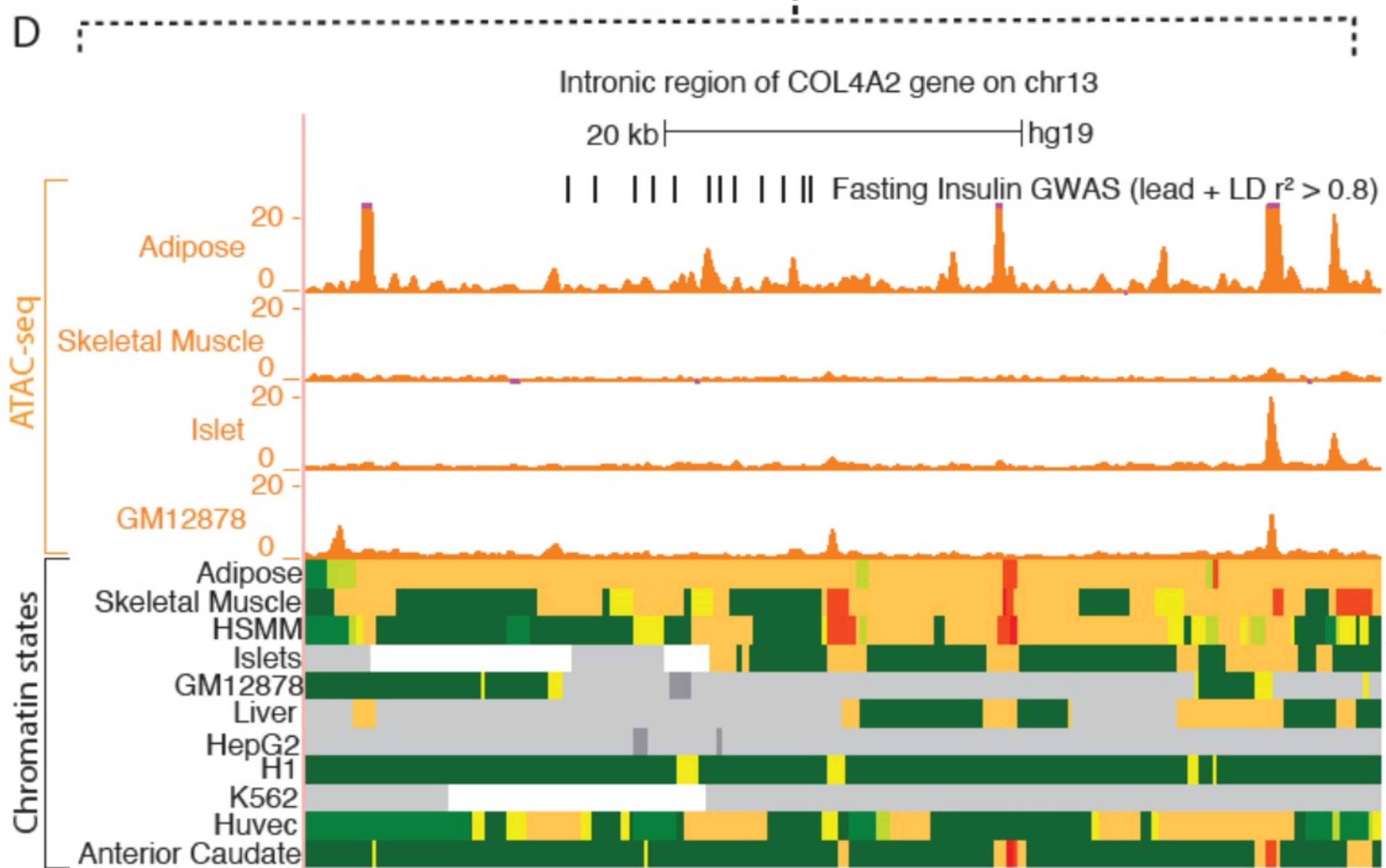
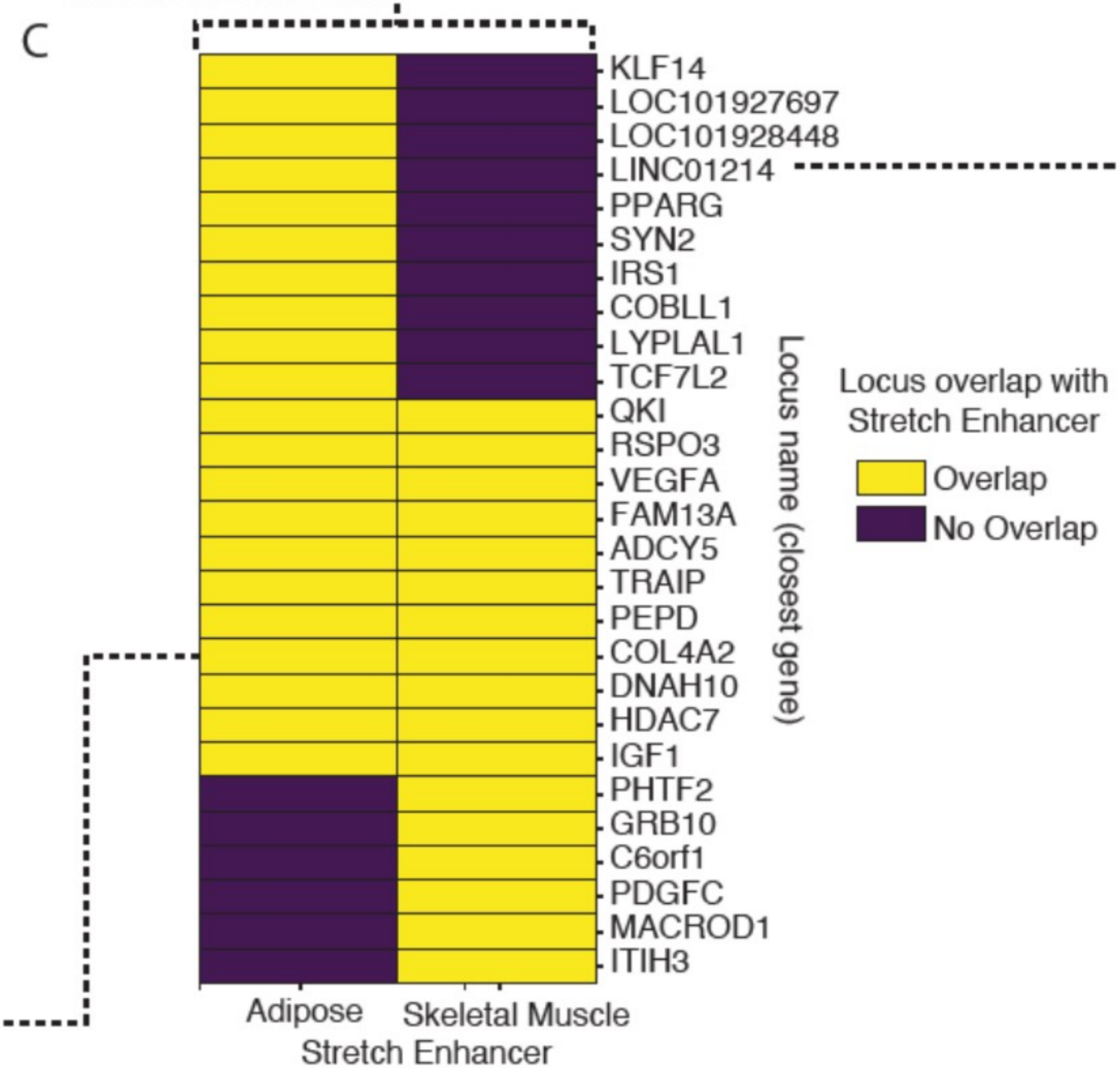
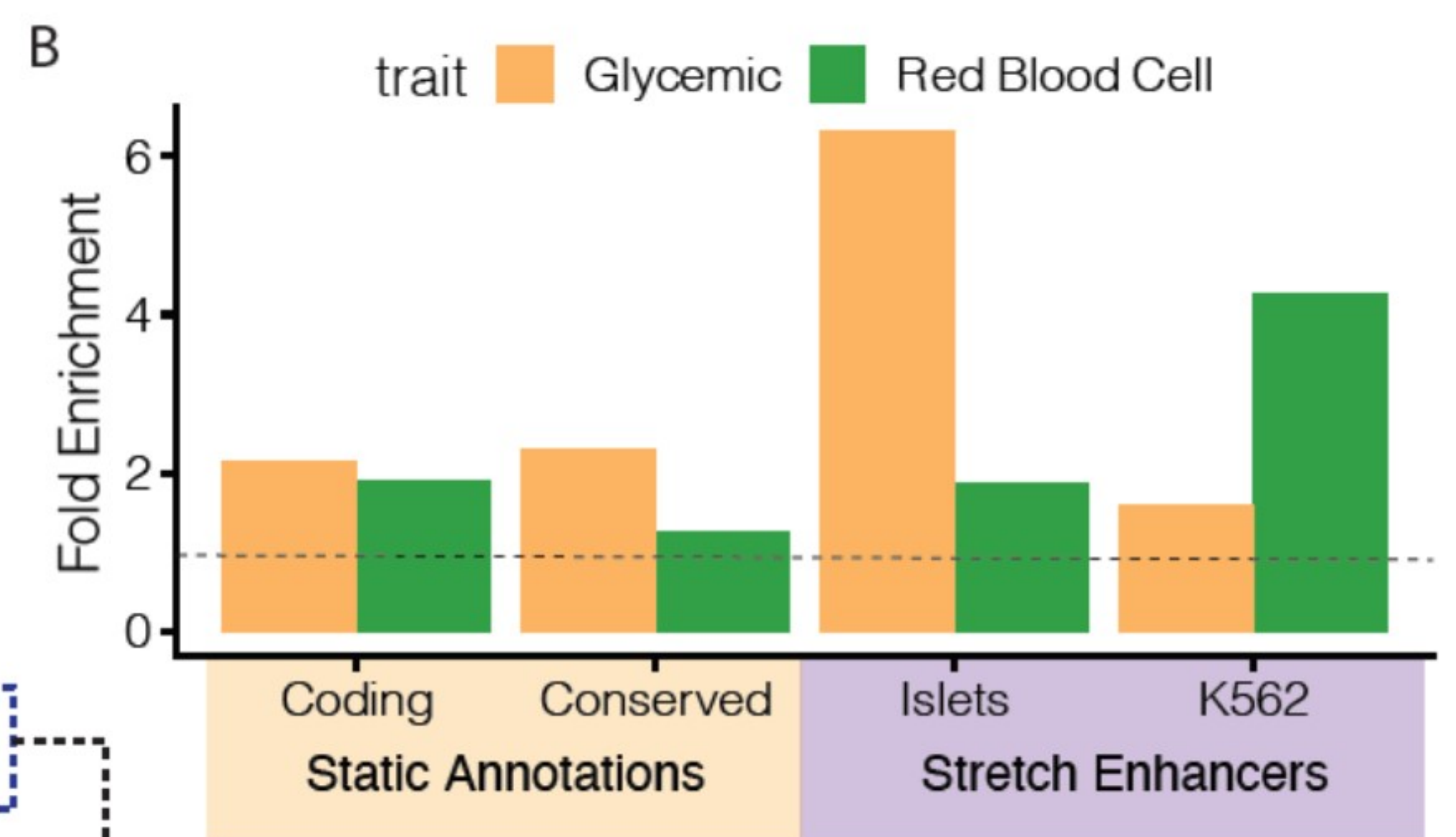
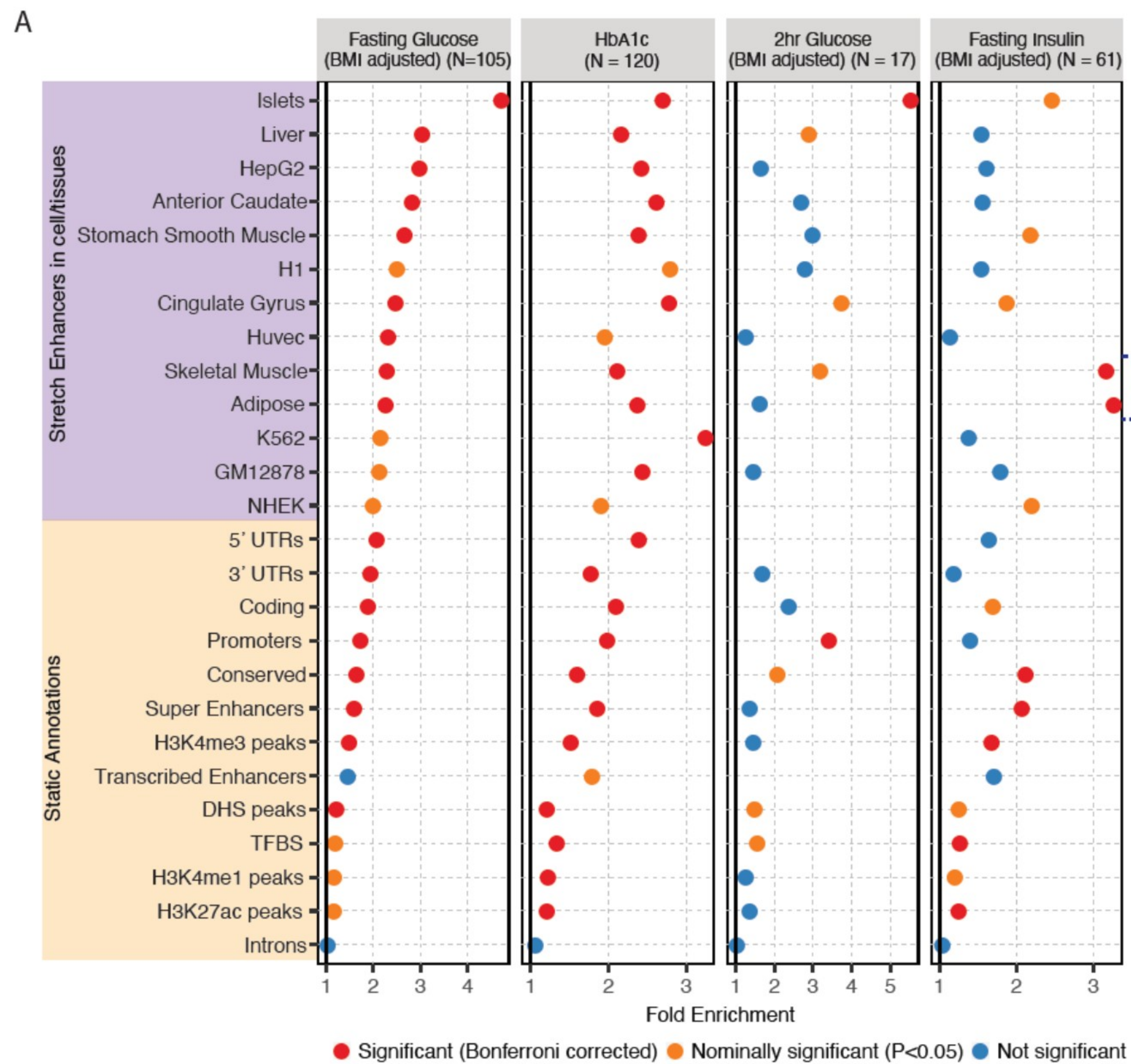


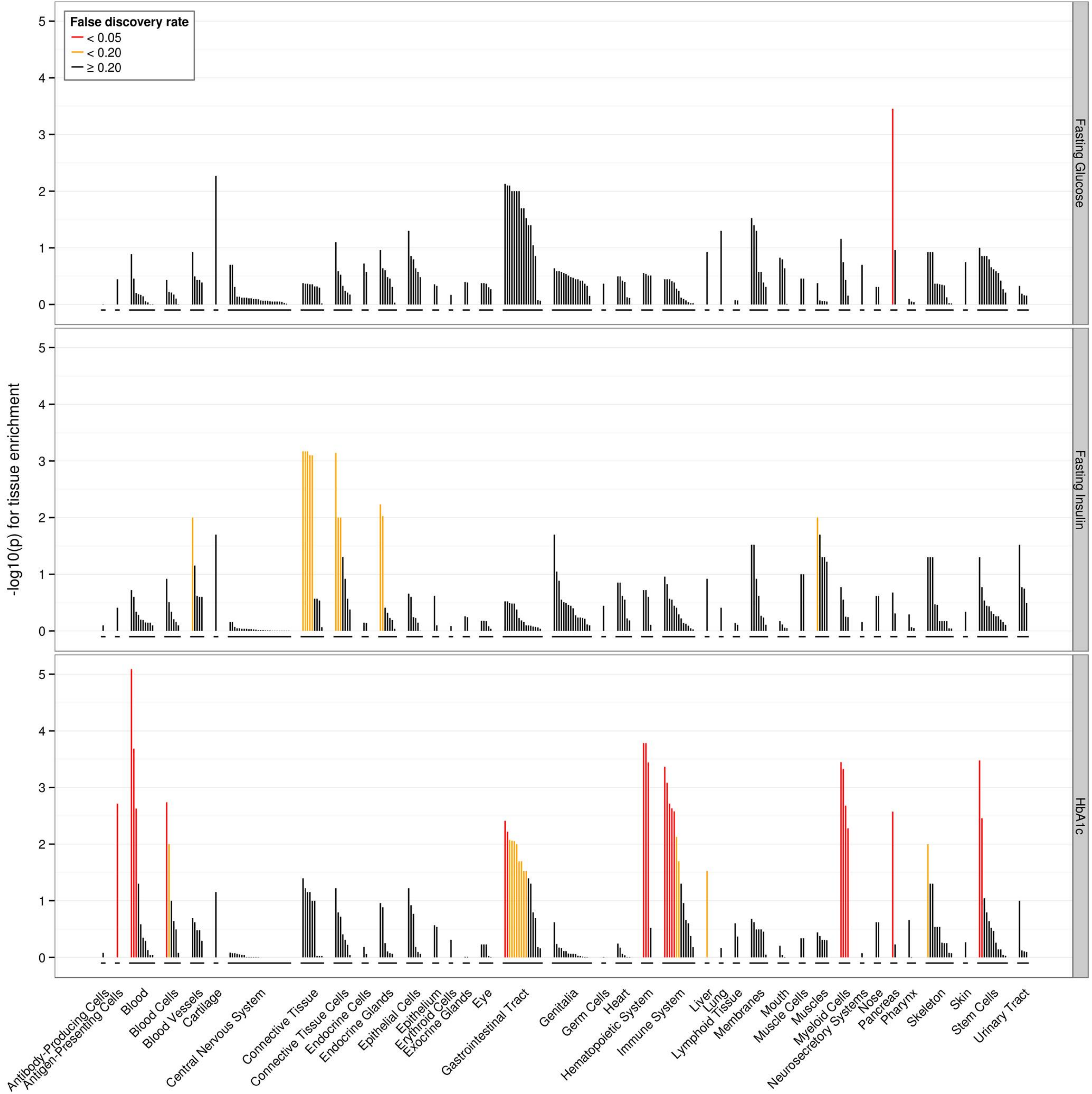
B. Number of variants at each 99% credible set

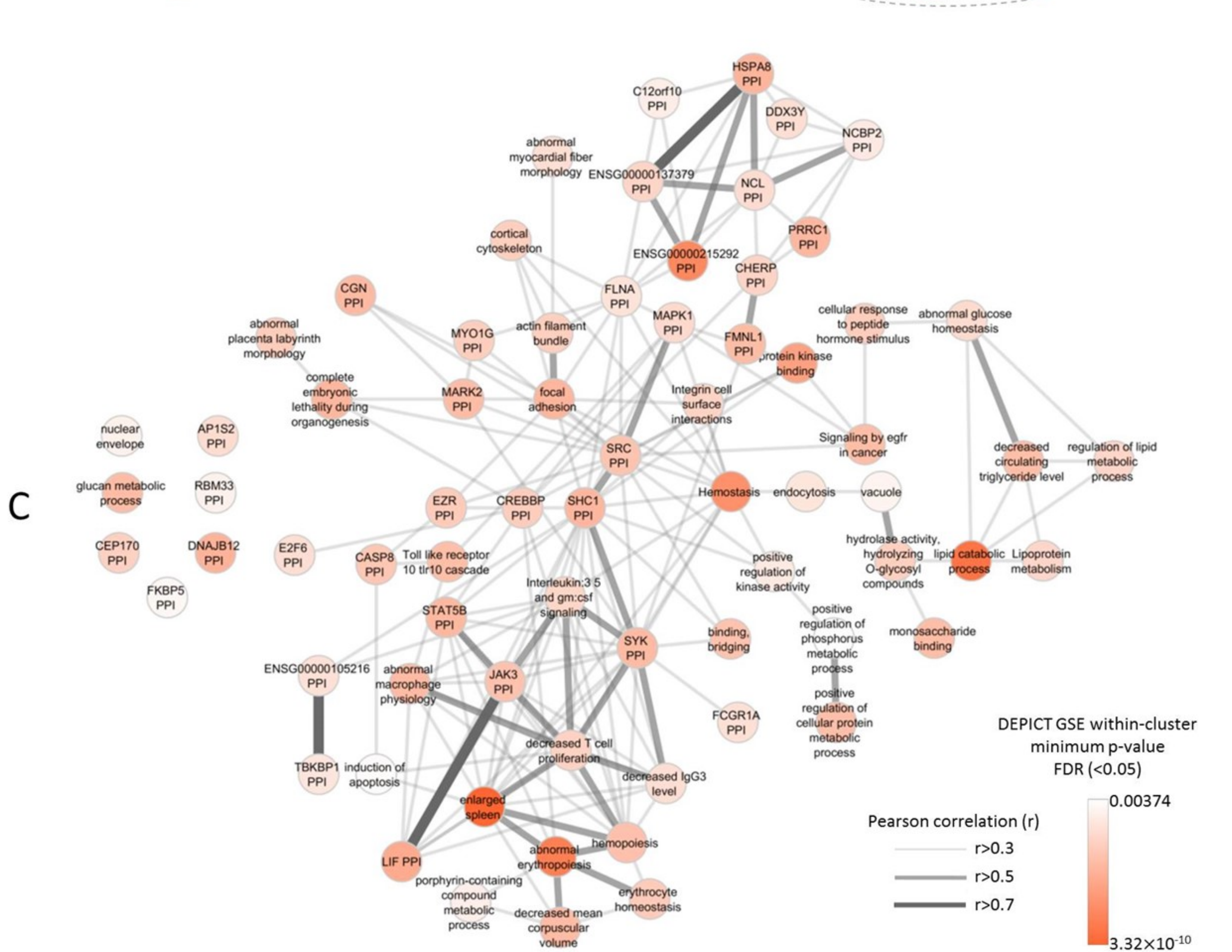
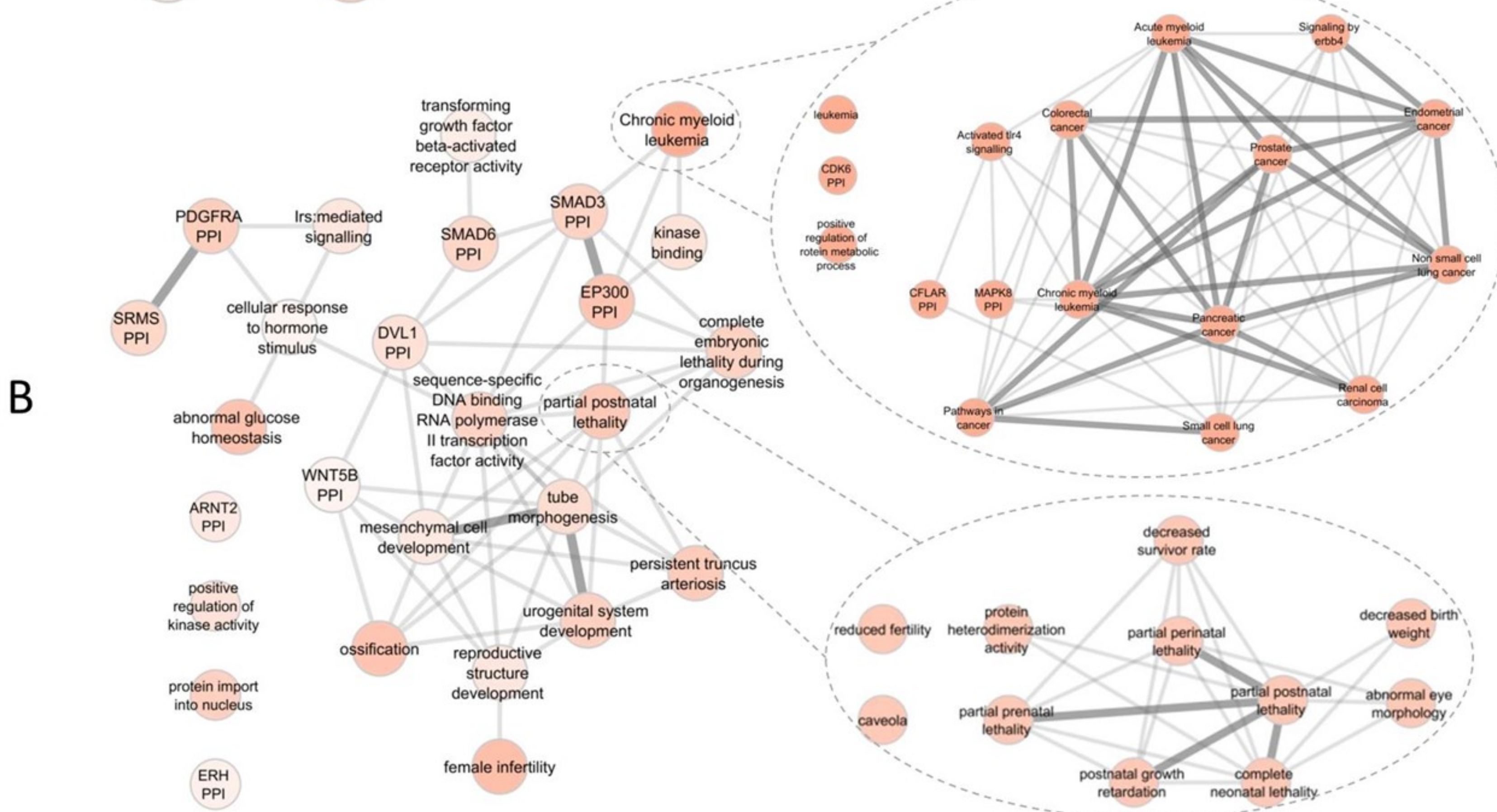
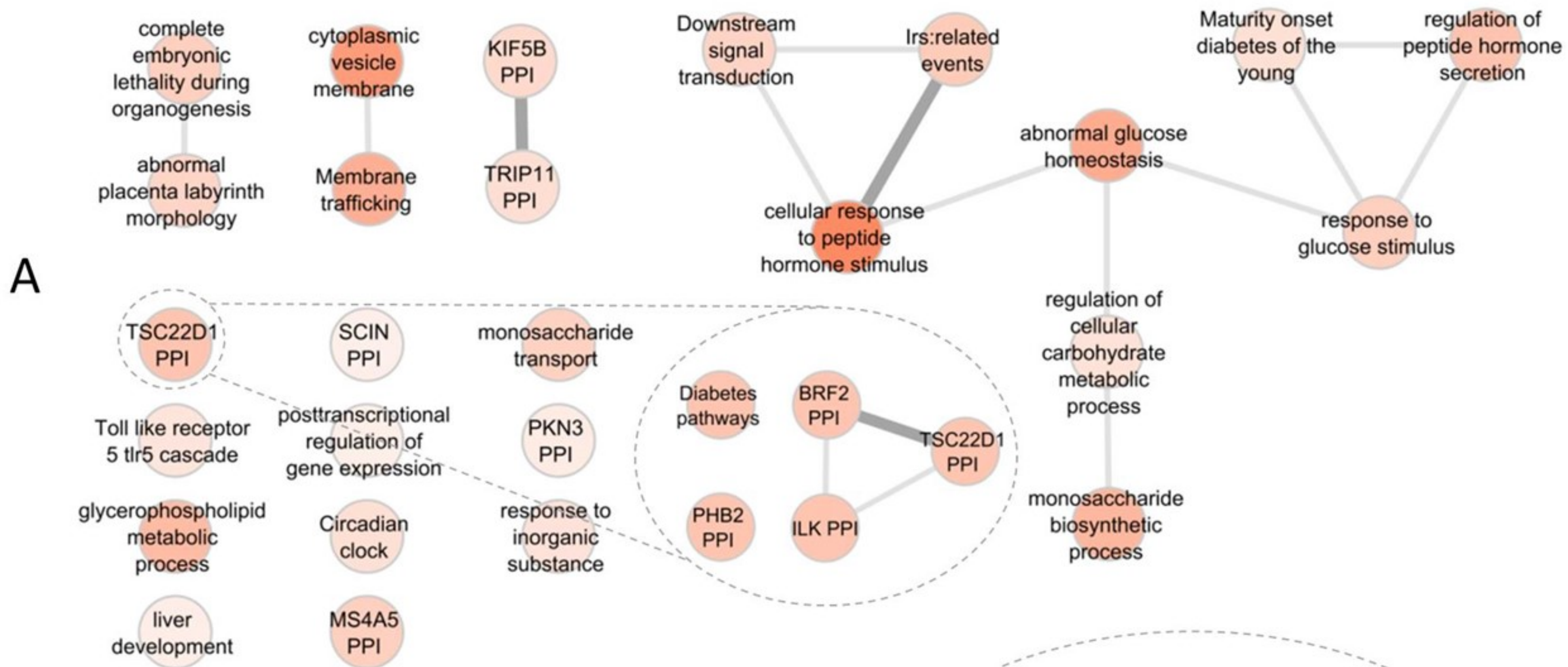


C. Fine-mapping resolution









Glossary Box

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

EA – 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.

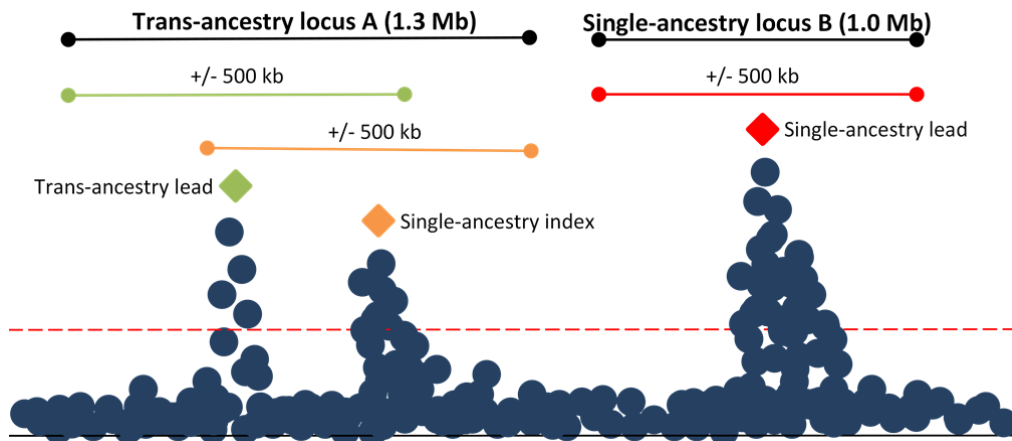
Single-ancestry index variants – variants identified by GCTA analysis of each autosome, and that appear to exert conditionally distinct effects on a given trait in a given ancestry ($P < 5 \times 10^{-8}$). As defined, these include the single-ancestry lead variant.

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 – a 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 - a 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 – As we expected some genetic variants to influence multiple correlated traits and that functional variants would influence traits across multiple ancestries, we combined results across traits and across ancestries into multi-trait trans-ancestry loci. A **trans-ancestry locus** is a genomic interval that contains trans-ancestry trait-specific lead variants, with/out additional single-ancestry index variants, for one or more trait. 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. 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.



Locus diagram – In this diagram, trans-ancestry locus A contains a trans-ancestry lead variant for one glycaemic trait represented by the green diamond, and another single-ancestry index variant for another glycaemic trait represented by the orange triangle. Single-ancestry locus B contains a single-ancestry lead variant represented by the red square. The orange, green and red bars represent a +/- 500Kb window around the orange, green, and red variants, respectively. The black bars indicate the full locus window where trans-ancestry locus A contains trans-ancestry lead and single-ancestry index variants for two traits and single-ancestry locus B has a single-ancestry lead variant for a single trait.