

# 1 Refining the accuracy of validated target 2 identification through coding variant fine- 3 mapping in type 2 diabetes

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413

414 **We aggregated coding variant data for 81,412 type 2 diabetes cases and 370,832 controls**  
415 **of diverse ancestry, identifying 40 coding variant association signals ( $p < 2.2 \times 10^{-7}$ ): of these,**  
416 **16 map outside known risk loci. We make two important observations. First, only five of**  
417 **these signals are driven by low-frequency variants: even for these, effect sizes are modest**  
418 **(odds ratio  $\leq 1.29$ ). Second, when we used large-scale genome-wide association data to**  
419 **fine-map the associated variants in their regional context, accounting for the global**  
420 **enrichment of complex trait associations in coding sequence, compelling evidence for**  
421 **coding variant causality was obtained for only 16 signals. At 13 others, the associated**  
422 **coding variants clearly represent “false leads” with potential to generate erroneous**  
423 **mechanistic inference. Coding variant associations offer a direct route to biological insight**  
424 **for complex diseases and identification of validated therapeutic targets: however,**  
425 **appropriate mechanistic inference requires careful specification of their causal**  
426 **contribution to disease predisposition.**

427

428       Genome-wide association studies (GWAS) have identified thousands of association  
429 signals influencing multifactorial traits such as type 2 diabetes (T2D) and obesity<sup>1-7</sup>. Most of  
430 these associations involve common variants that map to non-coding sequence, and  
431 identification of their cognate effector transcripts has proved challenging. Identification of  
432 coding variants causally implicated in trait predisposition offers a more direct route from  
433 association signal to biological inference.

434       The exome occupies 1.5% of overall genome sequence, but for many common diseases,  
435 coding variants make a disproportionate contribution to trait heritability<sup>8,9</sup>. This enrichment  
436 indicates that coding variant association signals have an enhanced probability of being  
437 causal when compared to those involving an otherwise equivalent non-coding variant. This  
438 does not, however, guarantee that all coding variant associations are causal. Alleles driving  
439 common-variant (minor allele frequency [MAF]  $\geq 5\%$ ) GWAS signals typically reside on  
440 extended risk haplotypes that, owing to linkage disequilibrium (LD), incorporate many  
441 common variants<sup>10,11</sup>. Consequently, the presence of a coding allele on the risk haplotype  
442 does not constitute sufficient evidence that it represents the causal variant at the locus, or  
443 that the gene within which it lies is mediating the association signal. Since much coding  
444 variant discovery has proceeded through exome-specific analyses (either exome-array  
445 genotyping or exome sequencing), researchers have often been poorly-placed to position

446 coding variant associations in the context of regional genetic variation. It is unclear how  
447 often this may have led to incorrect assumptions regarding their causal role.

448 In our recent study of T2D predisposition<sup>12</sup>, we surveyed the exomes of 34,809 T2D  
449 cases and 57,985 controls, of predominantly European descent, and identified 13 distinct  
450 coding variant associations reaching genome-wide significance. Twelve of these associations  
451 involved common variants, but the data hinted at a substantial pool of lower-frequency  
452 coding variants of moderate impact, potentially amenable to detection in larger samples.  
453 We also reported that, whilst many of these signals fell within common variant loci  
454 previously identified by GWAS, it was far from trivial to determine, using available data,  
455 whether those coding variants were causal or 'hitchhiking' on risk haplotypes.

456 Here, we report analyses that address these two issues. First, we extend the scope of  
457 our exome-array genotyping to include data from 81,412 T2D cases and 370,832 controls of  
458 diverse ancestry, substantially increasing power to detect coding variant associations across  
459 the allele-frequency spectrum. Second, to understand the extent to which identification of  
460 coding variant associations provides a reliable guide to causal mechanisms, we undertake  
461 high-resolution fine-mapping of identified coding variant association signals in 50,160 T2D  
462 cases and 465,272 controls of European ancestry with genome-wide genotyping data.

463

## 464 **RESULTS**

465

466 **Discovery study overview.** First, we set out to discover coding variant association signals by  
467 aggregating T2D association summary statistics in up to 452,244 individuals (effective  
468 sample size 228,825) across five ancestry groups, performing both European-specific (EUR)  
469 and trans-ethnic (TE) meta-analyses (**Supplementary Tables 1 and 2**). Analysis was  
470 restricted to the 247,470 variants represented on the exome-array. Genotypes were  
471 assembled from: (a) 58,425 cases and 188,032 controls genotyped with the exome-array; (b)  
472 14,608 cases and 174,322 controls from UK Biobank and GERA (Resource for Genetic  
473 Epidemiology on Adult Health and Aging) genotyped with GWAS arrays enriched for exome  
474 content and/or coverage of low-frequency variation across ethnic groups<sup>13,14</sup>; and (c) 8,379  
475 cases and 8,478 controls with whole-exome sequence from GoT2D/T2D-GENES<sup>12</sup> and  
476 SIGMA<sup>15</sup> studies. Overall, this represented a 3-fold increase in effective sample size over our  
477 previous study of T2D predisposition within coding sequence<sup>12</sup>. To deconvolute the impact

478 of obesity on T2D-associated variants, association analyses were conducted with and  
479 without body mass index (BMI) adjustment.

480 We considered  $p < 2.2 \times 10^{-7}$  as significant for protein truncating variants (PTVs) and  
481 moderate impact coding variants (including missense, in-frame indel and splice region  
482 variants) based on a weighted Bonferroni correction that accounts for the observed  
483 enrichment in complex trait association signals across sequence annotation<sup>16</sup>. This threshold  
484 matches those obtained through other approaches such as simple Bonferroni correction for  
485 the number of coding variants on the exome-array (**Methods**). Compared to our previous  
486 study<sup>12</sup>, the expanded sample size substantially increased power to detect association for  
487 common variants of modest effect (e.g. from 14.4% to 97.9% for a variant with 20% MAF  
488 and odds ratio [OR]=1.05) and lower-frequency variants with larger effects (e.g. from 11.8%  
489 to 97.5% for a variant with 1% MAF and OR=1.20) assuming homogenous allelic effects  
490 across ancestry groups (**Methods**).

491

492 **Insights into coding variant association signals underlying T2D susceptibility.** We detected  
493 significant associations at 69 coding variants under an additive genetic model (either in BMI  
494 unadjusted or adjusted analysis), mapping to 38 loci (**Supplementary Fig. 1, Supplementary**  
495 **Table 3**). We observed minimal evidence of heterogeneity in allelic OR between ancestry  
496 groups (**Supplementary Table 3**), and no compelling evidence for non-additive allelic effects  
497 (**Supplementary Fig. 2, Supplementary Table 4**). Reciprocal conditional analyses (**Methods**)  
498 indicated that the 69 coding variants represented 40 distinct association signals (conditional  
499  $p < 2.2 \times 10^{-7}$ ) across the 38 loci, with two distinct signals each at *HNF1A* and *RREB1*  
500 (**Supplementary Table 5**). These 40 signals included the 13 associations reported in our  
501 earlier publication<sup>12</sup>, each featuring more significant associations in this expanded meta-  
502 analysis (**Supplementary Table 6**). Twenty-five of the 40 signals were significant in both EUR  
503 and TE analyses. Of the other 15, three (*PLCB3*, *C17orf58*, and *ZHX3*) were significant in EUR,  
504 and all reached  $p_{TE} < 6.8 \times 10^{-6}$  in the TE analysis: for *PLCB3* and *ZHX3*, risk allele frequencies  
505 were substantially lower outside European descent populations. Twelve loci  
506 (**Supplementary Table 3**) were significant in TE alone, but for these (except *PAX4* which is  
507 East Asian specific), the evidence for association was proportionate in the smaller EUR  
508 component ( $p_{EUR} < 8.4 \times 10^{-5}$ ).

509 Sixteen of the 40 distinct association signals mapped outside regions previously  
510 implicated in T2D susceptibility (Methods, **Table 1**). These included missense variant signals  
511 in *POC5* (p.His36Arg, rs2307111,  $p_{TE}=1.6\times 10^{-15}$ ), *PNPLA3* (p.Ile148Met, rs738409,  $p_{TE}$  BMI-  
512 adjusted= $2.8\times 10^{-11}$ ), and *ZZEF1* (p.Ile2014Val, rs781831,  $p_{TE}=8.3\times 10^{-11}$ ).

513 In addition to the 69 coding variant signals, we detected significant ( $p<5\times 10^{-8}$ ) and  
514 novel T2D-associations for 20 non-coding variants (at 15 loci) that were also assayed on the  
515 exome-array (**Supplementary Table 7**). Three of these (*POC5*, *LPL*, and *BPTF*) overlap with  
516 novel coding signals reported here.

517

518 **Contribution of low-frequency and rare coding variation to T2D susceptibility.** Despite  
519 increased power and good coverage of low-frequency variants on the exome-array<sup>12</sup>, 35 of  
520 the 40 distinct coding variant association signals were common, with modest effects (allelic  
521 ORs 1.02-1.36) (**Supplementary Fig. 3, Supplementary Table 3**). The five signals attributable  
522 to lower-frequency variants were also of modest effect (allelic ORs 1.09-1.29)  
523 (**Supplementary Fig. 3**). Two of the lower-frequency variant signals were novel, and in both,  
524 the minor allele was protective against T2D: *FAM63A* p.Tyr95Asn (rs140386498, MAF=1.2%,  
525 OR= 0.82 [0.77-0.88],  $p_{EUR}=5.8\times 10^{-8}$ ) and *ANKH* p.Arg187Gln (rs146886108, MAF=0.4%,  
526 OR=0.78 [0.69-0.87],  $p_{EUR}=2.0\times 10^{-7}$ ). Both variants were very rare or monomorphic in non-  
527 European descent individuals.

528 In Fuchsberger et al.<sup>12</sup>, we highlighted a set of 100 low-frequency coding variants  
529 with allelic ORs between 1.10 and 2.66, which despite relatively large estimates for liability-  
530 scale variance explained, had not reached significance. In this expanded analysis, only five of  
531 these variants, including the two novel associations at *FAM63A* p.Tyr95Asn and *ANKH*  
532 p.Arg187Gln, attained significance. More precise effect-size estimation in the larger sample  
533 size indicates that OR estimates in the earlier study were subject to a substantial upwards  
534 bias (**Supplementary Fig. 3**).

535 To detect additional rare variant association signals, we performed gene-based  
536 analyses (burden and SKAT<sup>17</sup>) using previously-defined “strict” and “broad” masks, filtered  
537 for annotation and MAF<sup>12,18</sup> (**Methods**). We identified gene-based associations with T2D  
538 susceptibility ( $p<2.5\times 10^{-6}$ , Bonferroni correction for 20,000 genes) for *FAM63A* (10 variants,  
539 combined MAF=1.9%,  $p_{EUR}=3.1\times 10^{-9}$ ) and *PAM* (17 variants, combined MAF=4.7%,  
540  $p_{TE}=8.2\times 10^{-9}$ ). On conditional analysis (**Supplementary Table 8**), the gene-based signal at

541 *FAM63A* was entirely attributable to the low-frequency p.Tyr95Asn allele described earlier  
542 (conditional  $p=0.26_{EUR}$ ). The gene-based signal for *PAM* was also driven by a single low-  
543 frequency variant (p.Asp563Gly; conditional  $p_{TE}=0.15$ ). A second, previously-described, low-  
544 frequency variant, *PAM* p.Ser539Trp<sup>19</sup>, is not represented on the exome-array, and did not  
545 contribute to these analyses.

546

547 **Fine-mapping of coding variant association signals with T2D susceptibility.** These analyses  
548 identified 40 distinct coding variant associations with T2D, but this information is not  
549 sufficient to determine that these variants are causal for disease. To assess the role of these  
550 coding variants given regional genetic variation, we fine-mapped these association signals  
551 using a meta-analysis of 50,160 T2D cases and 465,272 controls (European-descent only;  
552 partially overlapping with the discovery samples), which we aggregated from 24 GWAS.  
553 Each component GWAS was imputed using appropriate high-density reference panels (for  
554 most, the Haplotype Reference Consortium<sup>20</sup>; **Methods, Supplementary Table 9**). Before  
555 fine-mapping, distinct association signals were delineated using approximate conditional  
556 analyses (**Methods, Supplementary Table 5**). We included 37 of the 40 identified coding  
557 variants in this fine-mapping analysis, excluding three (those at the *MHC*, *PAX4*, and *ZHX3*)  
558 that were, for various reasons (see **Methods**), not amenable to fine-mapping in the GWAS  
559 data.

560 For each of these 37 signals, we first constructed “functionally-unweighted” credible  
561 variant sets, which collectively account for 99% of the posterior probability of association  
562 (PPA), based exclusively on the meta-analysis summary statistics<sup>21</sup> (**Methods,**  
563 **Supplementary Table 10**). For each signal, we calculated the proportion of PPA attributable  
564 to coding variants (missense, in-frame indel, and splice region variants; **Figure 1,**  
565 **Supplementary Fig. 4 and 5**). There were only two signals at which coding variants  
566 accounted for  $\geq 80\%$  of PPA: *HNF4A* p.Thr139Ile (rs1800961, PPA $>0.999$ ) and *RREB1* p.  
567 Asp1171Asn (rs9379084, PPA=0.920). However, at other signals, including those for *GCKR*  
568 p.Pro446Leu and *SLC30A8* p.Arg276Trp, for which robust empirical evidence has established  
569 a causal role<sup>22,23</sup>, genetic support for coding variant causation was weak. This is because  
570 coding variants were typically in high LD ( $r^2>0.9$ ) with large numbers of non-coding variants,  
571 such that the PPA was distributed across many sites with broadly equivalent evidence for  
572 association.

573           These functionally-unweighted sets are based on genetic fine-mapping data alone,  
574 and do not account for the disproportionate representation of coding variants amongst  
575 GWAS associations for complex traits<sup>8,9</sup>. To accommodate this information, we extended the  
576 fine-mapping analyses by incorporating an “annotation-informed prior” model of causality.  
577 We derived priors from estimates of the enrichment of association signals by sequence  
578 annotation from analyses conducted by deCODE across 96 quantitative and 123 binary  
579 phenotypes<sup>16</sup> (**Methods**). This model “boosts” the prior, and hence the posterior  
580 probabilities (we use ‘ $\text{aiPPA}$ ’ to denote annotation-informed PPAs) of coding variants. It also  
581 takes account (in a tissue-non-specific manner) of the GWAS enrichment of variants within  
582 enhancer elements (as assayed through DNase I hypersensitivity) when compared to non-  
583 coding variants mapping elsewhere. The annotation-informed model generated smaller 99%  
584 credible sets across most signals, corresponding to fine-mapping at higher resolution  
585 (**Supplementary Table 10**). As expected, the contribution of coding variants was increased  
586 under the annotation-informed model. At these 37 association signals, we distinguished  
587 three broad patterns of causal relationships between coding variants and T2D risk.

588

589 **Group 1: T2D association signal is driven by coding variants.** At 16 of the 37 distinct signals,  
590 coding variation accounted for >80% of the  $\text{aiPPA}$  (**Fig. 1, Table 2, Supplementary Table 10**).  
591 This was attributable to a single coding variant at 12 signals and multiple coding variants at  
592 four. Reassuringly, group 1 signals confirmed coding variant causation for several loci (*GCKR*,  
593 *PAM*, *SLC30A8*, *KCNJ11-ABCC8*) at which functional studies have established strong  
594 mechanistic links to T2D pathogenesis (**Table 2**). T2D association signals at the 12 remaining  
595 signals (**Fig. 1, Supplementary Table 10**) had not previously been shown to be driven by  
596 coding variation, but our fine-mapping analyses pointed to causal coding variants with high  
597  $\text{aiPPA}$  values: these included *HNF4A*, *RREB1* (p. Asp1171Asn), *ANKH*, *WSCD2*, *POC5*, *TM6SF2*,  
598 *HNF1A* (p. Ala146Val; p. Ile75Leu), *GIPR*, *LPL*, *PLCB3*, and *PNPLA3* (**Table 2**). At several of  
599 these, independent evidence corroborates the causal role of the genes harbouring the  
600 associated coding variants. For example, rare coding mutations at *HNF1A* and *HNF4A* are  
601 causal for monogenic, early-onset forms of diabetes<sup>24</sup>; and at *TM6SF2* and *PNPLA3*, the  
602 associated coding variants are implicated in the development of non-alcoholic fatty liver  
603 disease (NAFLD)<sup>25,26</sup>.

604 The use of priors to capture the enrichment of coding variants seems a reasonable  
605 model, genome-wide. However, at any given locus, strong priors (especially for PTVs) might  
606 elevate to apparent causality, variants that would have been excluded from a causal role on  
607 the basis of genetic fine-mapping alone. Comparison of the annotation-informed and  
608 functionally-unweighted credible sets for group 1 signals indicated that this scenario was  
609 unlikely. For 11 of the 16 (*GCKR*, *PAM*, *KCNJ11-ABCC8*, *HNF4A*, *RREB1* [p.Asp1171Asn],  
610 *ANKH*, *POC5*, *TM6SF2*, *HNF1A* [p.Ala146Val], *PLCB3*, *PNPLA3*), the coding variant had the  
611 highest PPA in the fine-mapping analysis (**Table 2**) even under the functionally-unweighted  
612 model. At *SLC30A8*, *WSCD2*, and *GIPR*, the coding variants had similar PPAs to the lead non-  
613 coding SNPs under the functionally-unweighted prior (**Table 2**). At these 14 signals  
614 therefore, coding variants have either greater or equivalent PPA to the best flanking non-  
615 coding SNPs under the functionally-unweighted model, but receive a boost in PPA after  
616 incorporating the annotation weights.

617 The situation is less clear at *LPL*. Here, fine-mapping resolution is poor under the  
618 functionally-unweighted prior, and the coding variant sits on an extended haplotype in  
619 strong LD with non-coding variants, some with higher PPA, such as rs74855321 (PPA=0.048)  
620 (compared to *LPL* p.Ser474\* [rs328, PPA=0.023]). However, *LPL* p.Ser474\* is annotated as a  
621 PTV, and benefits from a substantially-increased prior that boosts its annotation-informed  
622 ranking (**Table 2**). Ultimately, decisions regarding the causal role of any such variant must  
623 rest on the amalgamation of evidence from diverse sources including detailed functional  
624 evaluation of the coding variants, and of other variants with which they are in LD.

625

626 **Group 2: T2D association signals are not attributable to coding variants.** At 13 of the 37  
627 distinct signals, coding variation accounted for <20% of the PPA, even after applying the  
628 annotation-informed prior model. These signals are likely to be driven by local non-coding  
629 variation and mediated through regulatory mechanisms. Five of these signals (*TPCN2*, *MLX*,  
630 *ZZEF1*, *C17orf58*, and *CEP68*) represent novel T2D-association signals identified in the  
631 exome-focused analysis. Given the exome-array discoveries, it would have been natural to  
632 consider the named genes at these, and other loci in this group, as candidates for mediation  
633 of their respective association signals. However, the fine-mapping analyses indicate that  
634 these coding variants do not provide useful mechanistic inference given low  $a_i$ PPA (**Fig. 1**,  
635 **Table 2**).

636 The coding variant association at the *CENTD2* (*ARAP1*) locus is a case-in-point. The  
637 association with the p.Gln802Glu variant in *ARAP1* (rs56200889,  $p_{TE}=4.8 \times 10^{-8}$  but  
638  $aiPPA < 0.001$ ) is seen in the fine-mapping analysis to be secondary to a substantially stronger  
639 non-coding association signal involving a cluster of variants including rs11603334  
640 ( $p_{TE}=9.5 \times 10^{-18}$ ,  $aiPPA=0.0692$ ) and rs1552224 ( $p_{TE}=2.5 \times 10^{-17}$ ,  $aiPPA=0.0941$ ). The identity of  
641 the effector transcript at this locus has been the subject of detailed investigation, and some  
642 early studies used islet expression data to promote *ARAP1*<sup>27</sup>. However, a more recent study  
643 integrating human islet genomics and murine gene knockout data establishes *STARD10* as  
644 the gene mediating the GWAS signal, consistent with the reassignment of the *ARAP1* coding  
645 variant association as irrelevant to causal inference<sup>28</sup>.

646 Whilst, at these loci, the coding variant associations represent “false leads”, this  
647 does not necessarily exclude the genes concerned from a causal role. At *WFS1* for example,  
648 coding variants too rare to be visible to the array-based analyses we performed, and  
649 statistically independent of the common p.Val333Ile variant we detected, cause an early-  
650 onset form of diabetes that renders *WFS1* the strongest local candidate for T2D  
651 predisposition.

652

653 **Group 3: Fine-mapping data consistent with partial role for coding variants.** At eight of the  
654 37 distinct signals, the  $aiPPA$  attributable to coding variation lay between 20% and 80%. At  
655 these signals, the evidence is consistent with “partial” contributions from coding variants,  
656 although the precise inference is likely to be locus-specific, dependent on subtle variations  
657 in LD, imputation accuracy, and the extent to which global priors accurately represent the  
658 functional impact of the specific variants concerned.

659 This group includes *PPARG* for which independent evidence corroborates the causal  
660 role of this specific effector transcript with respect to T2D-risk. *PPARG* encodes the target of  
661 antidiabetic thiazolidinedione drugs and harbours very rare coding variants causal for  
662 lipodystrophy and insulin resistance, conditions highly-relevant to T2D. The common variant  
663 association signal at this locus has generally been attributed to the p.Pro12Ala coding  
664 variant (rs1801282) although empirical evidence that this variant influences *PPARG* function  
665 is scant<sup>29-31</sup>. In the functionally-unweighted analysis, p.Pro12Ala had an unimpressive  $PPA$   
666 (0.0238); after including annotation-informed priors, the same variant emerged with the  
667 highest  $aiPPA$  (0.410), although the 99% credible set included 19 non-coding variants,

668 spanning 67kb (**Supplementary Table 10**). These credible set variants included rs4684847  
669 ( $a_iPPA=0.0089$ ), at which the T2D-associated allele has been reported to impact *PPARG2*  
670 expression and insulin sensitivity by altering binding of the homeobox transcription factor  
671 *PRRX1*<sup>32</sup>. These data are consistent with a model whereby regulatory variants contribute to  
672 altered *PPARG* activity in combination with, or potentially to the exclusion of, p.Pro12Ala.  
673 Future improvements in functional annotation for regulatory variants (gathered from  
674 relevant tissues and cell types) should provide increasingly granular priors that allow fine-  
675 tuned assignment of causality at loci such as this.

676

677 **Functional impact of coding alleles.** In other contexts, the functional impact of coding  
678 alleles is correlated with: (i) variant-specific features, including measures of conservation  
679 and predicted impact on protein structure; and (ii) gene-specific features such as extreme  
680 selective constraints as quantified by the intolerance to functional variation<sup>33</sup>. To determine  
681 whether similar measures could capture information pertinent to T2D causation, we  
682 compared coding variants falling into the different fine-mapping groups for a variety of  
683 measures including MAF, Combined Annotation Dependent Depletion (CADD) score<sup>34</sup>, and  
684 loss-of-function (LoF)-intolerance metric, pLI<sup>33</sup> (**Methods, Fig. 2**). Variants from group 1 had  
685 significantly higher CADD-scores than those in group 2 (Kolmogorov-Smirnov  $p=0.0031$ ).  
686 Except for the variants at *KCNJ11-ABCC8* and *GCKR*, all group 1 coding variants considered  
687 likely to be driving T2D association signals had CADD-score  $\geq 20$ . On this basis, we predict  
688 that the East-Asian specific coding variant at *PAX4*, for which the fine-mapping data were  
689 not informative, is also likely causal for T2D.

690

691 **T2D loci and physiological classification.** The development of T2D involves dysfunction of  
692 multiple mechanisms. Systematic analysis of the physiological effects of known T2D-risk  
693 alleles has improved understanding of the mechanisms through which they exert their  
694 primary impact on disease risk<sup>35</sup>. We obtained association summary statistics for diverse  
695 metabolic traits (and other outcomes) for 94 T2D-associated index variants. These 94 were  
696 restricted to sites represented on the exome-array and included the 40 coding signals plus  
697 54 distinct non-coding signals (12 novel and 42 previously-reported non-coding GWAS lead  
698 SNPs). We applied clustering techniques (**Methods**) to generate multi-trait association  
699 patterns, allocating 71 of the 94 loci to one of three main physiological categories

700 **(Supplementary Figs. 6, Supplementary Table 11)**. The first category, comprising nine T2D-  
701 risk loci with strong BMI and dyslipidemia associations, included three of the novel coding  
702 signals: *PNPLA3*, *POC5* and *BPTF*. The T2D associations at both *POC5* and *BPTF* were  
703 substantially attenuated ( $>2$ -fold decrease in  $-\log_{10}p$ ) after adjusting for BMI (**Table 1,**  
704 **Supplementary Table 3, Supplementary Fig. 7**), indicating that their impact on T2D-risk is  
705 likely mediated by a primary effect on adiposity. *PNPLA3* and *POC5* are established NAFLD<sup>25</sup>  
706 and BMI<sup>6</sup> loci, respectively. The second category featured 39 loci at which multi-trait profiles  
707 indicated a primary effect on insulin secretion. This set included four of the novel coding  
708 variant signals (*ANKH*, *ZZEF1*, *TTL6*, *ZHX3*). The third category encompassed 23 loci with  
709 primary effects on insulin action, including signals at the *KIF9*, *PLCB3*, *CEP68*, *TPCN2*,  
710 *FAM63A*, and *PIM3* loci. For most variants in this category, the T2D-risk allele was associated  
711 with lower BMI, and T2D association signals were more pronounced after adjustment for  
712 BMI. At a subset of these loci, including *KIF9* and *PLCB3*, T2D-risk alleles were associated  
713 with higher waist-hip ratio and lower body fat percentage, indicating that the mechanism of  
714 action likely reflects limitations in storage capacity of peripheral adipose tissue<sup>36</sup>.

715

## 716 **DISCUSSION**

717

718 The present study adds to mounting evidence constraining the contribution of lower-  
719 frequency variants to T2D-risk. Although the exome-array interrogates only a subset of the  
720 universe of coding variants, it captures the majority of low-frequency coding variants in  
721 European populations. The substantial increase in sample size in the present study over our  
722 previous effort<sup>12</sup> (effective sample sizes of 228,825 and 82,758, respectively), provides more  
723 robust evaluation of the effect size distribution in this low-frequency variant range, and  
724 indicates that previous analyses are likely, if anything, to have overestimated the  
725 contribution of low-frequency variants to T2D-risk.

726 The present study is less informative regarding rare variants. These are sparsely  
727 captured on the exome-array. In addition, the combination of greater regional diversity in  
728 rare allele distribution and the enormous sample sizes required to detect rare variant  
729 associations (likely to require meta-analysis of data from diverse populations) acts against  
730 their identification. Our complementary genome and exome sequence analyses have thus  
731 far failed to register strong evidence for a substantial rare variant component to T2D-risk<sup>12</sup>.

732 It is therefore highly unlikely that rare variants missed in our analyses are causal for any of  
733 the common or low-frequency variant associations we have detected and fine-mapped. On  
734 the other hand, it is probable that rare coding alleles, with associations that are distinct  
735 from the common variant signals we have examined and detected only through sequence  
736 based analyses, will provide additional clues to the most likely effector transcripts at some  
737 of these signals (*WFS1* provides one such example).

738         Once a coding variant association is detected, it is natural to assume a causal  
739 connection between that variant, the gene in which it sits, and the phenotype of interest.  
740 Whilst such assignments may be robust for many rare protein-truncating alleles, we  
741 demonstrate that this implicit assumption is often inaccurate, particularly for associations  
742 attributable to common, missense variants. A third of the coding variant associations we  
743 detected were, when assessed in the context of regional LD, highly unlikely to be causal. At  
744 these loci, the genes within which they reside are consequently deprived of their implied  
745 connection to disease risk, and attention redirected towards nearby non-coding variants  
746 and their impact on regional gene expression. As a group, coding variants we assign as  
747 causal are predicted to have a more deleterious impact on gene function than those that we  
748 exonerate, but, as in other settings, coding annotation methods lack both sensitivity and  
749 specificity. It is worth emphasising that empirical evidence that the associated coding allele  
750 is “functional” (i.e. can be shown to influence cognate gene function in some experimental  
751 assay) provides limited reassurance that the coding variant is responsible for the T2D  
752 association, unless that specific perturbation of gene function can itself be plausibly linked  
753 to the disease phenotype.

754         Our fine-mapping analyses make use of the observation that coding variants are  
755 globally enriched across GWAS signals<sup>8,9,16</sup> with greater prior probability of causality  
756 assigned to those with more severe impact on biological function. We assigned diminished  
757 priors to non-coding variants, with lowest support for those mapping outside of DNase I  
758 hypersensitive sites. The extent to which our findings corroborate previous assignments of  
759 causality (often substantiated by detailed, disease-appropriate functional assessment and  
760 other orthogonal evidence) suggests that even these sparse annotations provide valuable  
761 information to guide target validation. Nevertheless, there are inevitable limits to the  
762 extrapolation of these ‘broad-brush’ genome-wide enrichments to individual loci:  
763 improvements in functional annotation for both coding and regulatory variants, particularly

764 when gathered from trait-relevant tissues and cell types, should provide more granular,  
765 trait-specific priors to fine-tune assignment of causality within associated regions. These will  
766 motivate target validation efforts that benefit from synthesis of both coding and regulatory  
767 mechanisms of gene perturbation. It also needs to be acknowledged that, without whole  
768 genome sequencing data on sample sizes comparable to those we have examined here,  
769 imperfections arising from the imputation may confound fine-mapping precision at some  
770 loci, and that robust inference will inevitably depend on integration of diverse sources of  
771 genetic, genomic and functional data.

772 The term “smoking gun” has often been used to describe the potential of functional  
773 coding variants to provide causal inference with respect to pathogenetic mechanisms<sup>37</sup>. This  
774 study provides a timely reminder that, even when a suspect with a smoking gun is found at  
775 the scene of a crime, it should not be assumed that they fired the fatal bullet.

776

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780

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818

## 819 **DISCLOSURES**

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924  
925

926 **FIGURE LEGENDS**

927

928 **Figure 1 | Posterior probabilities for coding variants across loci with annotation-informed**

929 **priors.** Fine-mapping of 37 distinct association signals was performed using European  
930 ancestry GWAS meta-analysis including 50,160 T2D cases and 465,272 controls. For each  
931 signal, we constructed a credible set of variants accounting for 99% of the posterior  
932 probability of driving the association, incorporating an “annotation informed” prior model  
933 of causality which “boosts” the posterior probability of driving the association signal that is  
934 attributed to coding variants. Each bar represents a signal with the total probability  
935 attributed to the coding variants within the 99% credible set plotted on the y-axis. When the  
936 probability (bar) is split across multiple coding variants (at least 0.05 probability attributed  
937 to a variant) at a particular locus, these are indicated by blue, pink, yellow, and green  
938 colours. The combined probability of the remaining coding variants is highlighted in grey.

939 *RREB1(a): RREB1 p. Asp1171Asn; RREB1(b): RREB1 p.Ser1499Tyr; HNF1A(a): HNF1A*  
940 *p.Ala146Val; HNF1A(b): HNF1A p.Ile75Leu; PPIP5K2† : PPIP5K2 p.Ser1207Gly; MTMR3†:*  
941 *MTMR3 p.Asn960Ser; IL17REL†: IL17REL p.Gly70Arg; NBEAL2†: NBEAL2 p.Arg511Gly, KIF9†:*  
942 *KIF9 p.Arg638Trp.*

943

944 **Figure 2 | Plot of measures of variant-specific and gene-specific features of distinct coding**  
945 **signals to assess the functional impact of coding alleles.** Each point represents a coding

946 variant with the minor allele frequency plotted on the x-axis and the Combined Annotation  
947 Dependent Depletion score (CADD-score) plotted on the y-axis. Size of each point varies  
948 with the measure of intolerance of the gene to loss of function variants (pLI) and the colour  
949 represents the fine-mapping group each variant is assigned to. Group 1: signal is driven by  
950 coding variant. Group 2: signal attributable to non-coding variants. Group 3: consistent with  
951 partial role for coding variants. Group 4: Unclassified category; includes *PAX4*, *ZHX3*, and  
952 signal at *TCF19* within the MHC region where we did not perform fine-mapping. Inset: plot  
953 shows the distribution of CADD-score between different groups. The plot is a combination  
954 of violin plots and box plots; width of each violin indicates frequency at the corresponding  
955 CADD-score and box plots show the median and the 25% and 75% quantiles. *P* value  
956 indicates significance from two-sample Kolmogorov-Smirnov test.

957

958 **Table 1 | Summary of discovery and fine-mapping analyses of the 40 index coding variants associated with T2D ( $p < 2.2 \times 10^{-7}$ ).**

Discovery meta-analysis using exome-array component: 81,412 T2D cases and 370,832 controls from diverse ancestries														Fine-mapping meta-analysis using GWAS: 50,160 T2D cases and 465,272 controls from European ancestry						
Locus	Index variant	rs ID	Chr	Pos	Alleles R/O	RAF	BMI unadjusted				BMI adjusted				RAF	OR	L95	U95	p-value	Group
							OR	L95	U95	p-value	OR	L95	U95	p-value						
<b>Previously reported T2D associated loci</b>																				
<i>MACF1</i>	<i>MACF1</i> p.Met1424Val	rs2296172	1	39,835,817	G/A	0.193	1.06	1.05	1.08	$6.7 \times 10^{-16}$	1.04	1.03	1.06	$5.9 \times 10^{-8}$	0.22	1.08	1.06	1.1	$1.6 \times 10^{-15}$	3
<i>GCKR</i>	<i>GCKR</i> p.Pro446Leu	rs1260326	2	27,730,940	C/T	0.630	1.06	1.05	1.08	$5.3 \times 10^{-25}$	1.06	1.04	1.07	$3.2 \times 10^{-18}$	0.607	1.05	1.04	1.07	$9.1 \times 10^{-10}$	1
<i>THADA</i>	<i>THADA</i> p.Cys845Tyr	rs35720761	2	43,519,977	C/T	0.895	1.08	1.05	1.1	$4.6 \times 10^{-15}$	1.07	1.05	1.10	$8.3 \times 10^{-16}$	0.881	1.1	1.07	1.12	$3.4 \times 10^{-12}$	2
<i>GRB14</i>	<i>COBL1</i> p.Asn901Asp	rs7607980	2	165,551,201	T/C	0.879	1.08	1.06	1.11	$8.6 \times 10^{-20}$	1.09	1.07	1.12	$5.0 \times 10^{-23}$	0.871	1.08	1.06	1.11	$3.6 \times 10^{-10}$	2
<i>PPARG</i>	<i>PPARG</i> p.Pro12Ala	rs1801282	3	12,393,125	C/G	0.887	1.09	1.07	1.11	$1.4 \times 10^{-17}$	1.10	1.07	1.12	$2.7 \times 10^{-19}$	0.876	1.12	1.09	1.14	$3.7 \times 10^{-17}$	3
<i>IGFBP2</i>	<i>SEN2</i> p.Thr291Lys	rs6762208	3	185,331,165	A/C	0.367	1.03	1.01	1.04	$1.6 \times 10^{-6}$	1.03	1.02	1.05	$3.0 \times 10^{-8}$	0.339	1.02	1.01	1.04	0.01	2
<i>WFS1</i>	<i>WFS1</i> p.Val333Ile	rs1801212	4	6,302,519	A/G	0.748	1.07	1.06	1.09	$1.1 \times 10^{-24}$	1.07	1.05	1.08	$7.1 \times 10^{-21}$	0.703	1.07	1.05	1.09	$4.1 \times 10^{-13}$	2
<i>PAM-PIP5K2</i>	<i>PAM</i> p.Asp336Gly	rs35658696	5	102,338,811	G/A	0.045	1.13	1.10	1.17	$1.2 \times 10^{-16}$	1.13	1.09	1.17	$7.4 \times 10^{-15}$	0.051	1.17	1.13	1.22	$2.5 \times 10^{-17}$	1
<i>RREB1</i>	<i>RREB1</i> p.Asp1171Asn	rs9379084	6	7,231,843	G/A	0.884	1.08	1.06	1.11	$1.1 \times 10^{-13}$	1.10	1.07	1.13	$1.5 \times 10^{-17}$	0.888	1.09	1.06	1.12	$1.1 \times 10^{-9}$	1
	<i>RREB1</i> p.Ser1499Tyr	rs35742417	6	7,247,344	C/A	0.836	1.04	1.03	1.06	$5.5 \times 10^{-8}$	1.04	1.02	1.06	$2.2 \times 10^{-7}$	0.817	1.04	1.02	1.07	0.00012	2
<i>MHC</i>	<i>TCF19</i> p.Met131Val	rs2073721	6	31,129,616	G/A	0.749	1.04	1.02	1.05	$1.6 \times 10^{-10}$	1.04	1.02	1.05	$2.3 \times 10^{-9}$	N/A	N/A	N/A	N/A	N/A	N/A
<i>PAX4</i>	<i>PAX4</i> p.Arg190His	rs2233580	7	127,253,550	T/C	0.029	1.36	1.25	1.48	$1.8 \times 10^{-12}$	1.38	1.26	1.51	$4.2 \times 10^{-13}$	0	N/A	N/A	N/A	N/A	N/A
<i>SLC30A8</i>	<i>SLC30A8</i> p.Arg276Trp	rs13266634	8	118,184,783	C/T	0.691	1.09	1.08	1.11	$1.9 \times 10^{-47}$	1.09	1.08	1.11	$1.3 \times 10^{-47}$	0.683	1.12	1.1	1.14	$8.2 \times 10^{-36}$	1
<i>GPSM1</i>	<i>GPSM1</i> p.Ser391Leu	rs60980157	9	139,235,415	C/T	0.771	1.06	1.05	1.08	$3.2 \times 10^{-16}$	1.06	1.05	1.08	$6.6 \times 10^{-16}$	0.756	1.06	1.04	1.09	$8.3 \times 10^{-8}$	3
<i>KCNJ11-ABCC8</i>	<i>KCNJ11</i> p.Lys29Glu	rs5219	11	17,409,572	T/C	0.364	1.06	1.05	1.07	$5.7 \times 10^{-22}$	1.07	1.05	1.08	$1.5 \times 10^{-22}$	0.381	1.07	1.05	1.09	$8.1 \times 10^{-16}$	1
<i>CENTD2</i>	<i>ARAP1</i> p.Gln802Glu	rs56200889	11	72,408,055	G/C	0.733	1.04	1.02	1.05	$4.8 \times 10^{-8}$	1.05	1.03	1.06	$5.2 \times 10^{-10}$	0.727	1.05	1.03	1.07	$2.3 \times 10^{-8}$	2
<i>KLHDC5</i>	<i>MRPS35</i> p.Gly43Arg	rs1127787	12	27,867,727	G/A	0.850	1.06	1.04	1.08	$1.4 \times 10^{-11}$	1.05	1.03	1.07	$1.5 \times 10^{-8}$	0.842	1.06	1.04	1.09	$2.2 \times 10^{-7}$	2
<i>HNF1A</i>	<i>HNF1A</i> p.Ile75Leu	rs1169288	12	121,416,650	C/A	0.323	1.04	1.03	1.06	$1.1 \times 10^{-11}$	1.04	1.02	1.06	$1.9 \times 10^{-10}$	0.33	1.05	1.04	1.07	$4.6 \times 10^{-9}$	1
	<i>HNF1A</i> p.Ala146Val	rs1800574	12	121,416,864	T/C	0.029	1.11	1.06	1.15	$6.1 \times 10^{-8}$	1.10	1.06	1.15	$1.3 \times 10^{-7}$	0.03	1.16	1.1	1.21	$5.0 \times 10^{-9}$	1
<i>MPHOSPH9</i>	<i>SBNO1</i> p.Ser729Asn	rs1060105	12	123,806,219	C/T	0.815	1.04	1.02	1.06	$5.7 \times 10^{-7}$	1.04	1.02	1.06	$1.1 \times 10^{-7}$	0.787	1.04	1.02	1.06	$3.6 \times 10^{-5}$	2
<i>CILP2</i>	<i>TM6SF2</i> p.Glu167Lys	rs58542926	19	19,379,549	T/C	0.076	1.07	1.05	1.10	$4.8 \times 10^{-12}$	1.09	1.06	1.11	$3.4 \times 10^{-15}$	0.076	1.09	1.05	1.12	$2.0 \times 10^{-7}$	1
<i>GIPR</i>	<i>GIPR</i> p.Glu318Gln	rs1800437	19	46,181,392	C/G	0.200	1.03	1.02	1.05	$7.1 \times 10^{-5}$	1.06	1.04	1.07	$6.8 \times 10^{-12}$	0.213	1.09	1.06	1.12	$4.6 \times 10^{-9}$	1
<i>HNF4A</i>	<i>HNF4A</i> p.Thr139Ile	rs1800961	20	43,042,364	T/C	0.032	1.09	1.05	1.13	$2.6 \times 10^{-8}$	1.10	1.06	1.14	$5.0 \times 10^{-8}$	0.037	1.17	1.12	1.22	$1.4 \times 10^{-12}$	1
<i>MTMR3-ASCC2</i>	<i>ASCC2</i> p.Asp407His	rs28265	22	30,200,761	C/G	0.925	1.09	1.06	1.11	$2.1 \times 10^{-12}$	1.09	1.07	1.12	$4.4 \times 10^{-14}$	0.916	1.1	1.07	1.14	$9.6 \times 10^{-11}$	3
<b>Novel T2D associated loci</b>																				
<i>FAM63A</i>	<i>FAM63A</i> p.Tyr95Asn	rs140386498	1	150,972,959	A/T	0.988	1.21	1.14	1.28	$7.5 \times 10^{-8}$	1.19	1.12	1.26	$6.7 \times 10^{-7}$	0.986	1.15	1.06	1.25	0.00047	3
<i>CEP68</i>	<i>CEP68</i> p.Gly74Ser	rs7572857	2	65,296,798	G/A	0.846	1.05	1.04	1.07	$8.3 \times 10^{-9}$	1.05	1.03	1.07	$6.6 \times 10^{-7}$	0.830	1.06	1.03	1.08	$6.6 \times 10^{-7}$	2
<i>KIF9</i>	<i>KIF9</i> p.Arg638Trp	rs2276853	3	47,282,303	A/G	0.588	1.02	1.01	1.04	$8.0 \times 10^{-5}$	1.03	1.02	1.05	$5.3 \times 10^{-8}$	0.602	1.04	1.02	1.05	$2.6 \times 10^{-5}$	3
<i>ANKH</i>	<i>ANKH</i> p.Arg187Gln	rs146886108	5	14,751,305	C/T	0.996	1.29	1.16	1.45	$1.4 \times 10^{-7}$	1.27	1.13	1.41	$3.5 \times 10^{-7}$	0.995	1.51	1.29	1.77	$3.5 \times 10^{-7}$	1
<i>POC5</i>	<i>POC5</i> p.His36Arg	rs2307111	5	75,003,678	T/C	0.562	1.05	1.04	1.07	$1.6 \times 10^{-15}$	1.03	1.01	1.04	$2.1 \times 10^{-5}$	0.606	1.06	1.05	1.08	$1.1 \times 10^{-12}$	1
<i>LPL</i>	<i>LPL</i> p.Ser474*	rs328	8	19,819,724	C/G	0.903	1.05	1.03	1.08	$6.8 \times 10^{-9}$	1.05	1.03	1.07	$2.3 \times 10^{-7}$	0.901	1.08	1.05	1.11	$7.1 \times 10^{-8}$	1
<i>PLCB3<sup>†</sup></i>	<i>PLCB3</i> p.Ser778Leu	rs35169799	11	64,031,241	T/C	0.071	1.05	1.02	1.08	$1.3 \times 10^{-5}$	1.06	1.03	1.09	$1.8 \times 10^{-7}$	0.065	1.07	1.04	1.11	$3.8 \times 10^{-5}$	1
<i>TPCN2</i>	<i>TPCN2</i> p.Val219Ile	rs72928978	11	68,831,364	G/A	0.890	1.05	1.02	1.07	$5.2 \times 10^{-7}$	1.05	1.03	1.07	$1.8 \times 10^{-8}$	0.847	1.03	1.00	1.05	0.042	2
<i>WSCD2</i>	<i>WSCD2</i> p.Thr113Ile	rs3764002	12	108,618,630	C/T	0.719	1.03	1.02	1.05	$3.3 \times 10^{-8}$	1.03	1.02	1.05	$1.2 \times 10^{-7}$	0.736	1.05	1.03	1.07	$8.1 \times 10^{-7}$	1
<i>ZZEF1</i>	<i>ZZEF1</i> p.Ile402Val	rs781831	17	3,947,644	C/T	0.422	1.04	1.03	1.05	$8.3 \times 10^{-11}$	1.03	1.02	1.05	$1.8 \times 10^{-7}$	0.407	1.04	1.02	1.05	$2.1 \times 10^{-5}$	2
<i>MLX</i>	<i>MLX</i> p.Gln139Arg	rs665268	17	40,722,029	G/A	0.294	1.04	1.02	1.05	$2.0 \times 10^{-8}$	1.03	1.02	1.04	$1.1 \times 10^{-5}$	0.280	1.04	1.02	1.06	$5.2 \times 10^{-6}$	2

<i>TLL6</i>	<i>TLL6</i> p.Glu712Asp	rs2032844	17	46,847,364	C/A	0.754	1.04	1.02	1.06	1.2x10 <sup>-7</sup>	1.03	1.01	1.04	0.00098	0.750	1.04	1.02	1.06	9.5x10 <sup>-5</sup>	3
<i>C17orf58</i> <sup>†</sup>	<i>C17orf58</i> p.Ile92Val	rs9891146	17	65,988,049	T/C	0.277	1.04	1.02	1.06	1.3x10 <sup>-7</sup>	1.02	1.00	1.04	0.00058	0.269	1.05	1.03	1.07	1.7x10 <sup>-7</sup>	2
<i>ZHX3</i> <sup>†</sup>	<i>ZHX3</i> p.Asn310Ser	rs17265513	20	39,832,628	C/T	0.211	1.05	1.03	1.07	9.2x10 <sup>-8</sup>	1.04	1.02	1.05	2.9x10 <sup>-6</sup>	0.208	1.02	1.00	1.04	0.068	N/A
<i>PNPLA3</i>	<i>PNPLA3</i> p.Ile148Met	rs738409	22	44,324,727	G/C	0.239	1.04	1.03	1.05	2.1x10 <sup>-10</sup>	1.05	1.03	1.06	2.8x10 <sup>-11</sup>	0.230	1.05	1.03	1.07	5.8x10 <sup>-6</sup>	1
<i>PIM3</i>	<i>PIM3</i> p.Val300Ala	rs4077129	22	50,356,693	T/C	0.276	1.04	1.02	1.05	1.9x10 <sup>-7</sup>	1.04	1.02	1.06	3.5x10 <sup>-8</sup>	0.280	1.04	1.02	1.06	8.7x10 <sup>-5</sup>	3

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960 Chr: chromosome. Pos: Position build 37. RAF: risk allele frequency. R: risk allele. O: other allele. BMI: body mass index. OR: odds ratio. L95: lower 95% confidence interval.

961 U95: upper 95% confidence interval. GWAS: genome wide association studies.<sup>†</sup>Summary statistics from European ancestry specific meta-analyses of 48,286 cases and

962 250,671 controls. Fine-mapping group 1: signal is driven by coding variant, group 2: signal attributable to non-coding variants, and group 3: consistent with partial role for

963 coding variants. *p*-values are based on the meta-analyses of discovery stage and fine-mapping studies as appropriate.

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970 **Table 2 | Posterior probabilities for coding variants within 99% credible set across loci**  
971 **with annotation-informed and functionally-unweighted prior based on fine-mapping**  
972 **analysis performed using 50,160 T2D cases and 465,272 controls of European ancestry.**  
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Locus	Variant	rs ID	Chr	Position	Posterior probability		Cumulative posterior probability attributed to coding variants	
					PPA	aiPPA	PPA	aiPPA
MACF1	MACF1 p.Ile39Val	rs16826069	1	39,797,055	0.012	0.240	0.032	0.628
	<b>MACF1 p.Met1424Val</b>	<b>rs2296172</b>	<b>1</b>	<b>39,835,817</b>	0.011	0.224		
	MACF1 p.Lys1625Asn	rs41270807	1	39,801,815	0.008	0.163		
FAM63A	FAM63A p.Tyr95Asn	rs140386498	1	150,972,959	0.005	0.129	0.012	0.303
GCKR	GCKR p. Pro 446Leu	rs1260326	2	27,730,940	0.773	0.995	0.773	0.995
THADA	<b>THADA p.Cys845Tyr</b>	<b>rs35720761</b>	<b>2</b>	<b>43,519,977</b>	<b>&lt;0.001</b>	<b>0.011</b>	0.003	0.120
	THADA p.Thr897Ala	rs7578597	2	43,732,823	0.003	0.107		
CEP68	CEP68 p.Gly74Ser	rs7572857	2	65,296,798	<0.001	0.004	<0.001	0.004
GRB14	COBL1 p.Asn901Asp	rs7607980	2	165,551,201	0.006	0.160	0.006	0.160
PPARG	PPARG p.Pro12Ala	rs1801282	3	12,393,125	0.023	0.410	0.024	0.410
KIF9	SETD2 p.Pro1962Lys	rs4082155	3	47,125,385	0.008	0.171	0.018	0.384
	NBEAL2 p.Arg511Gly	rs11720139	3	47,036,756	0.005	0.097		
	<b>KIF9 p.Arg638Trp</b>	<b>rs2276853</b>	<b>3</b>	<b>47,282,303</b>	0.003	0.059		
IGF2BP2	SEN2 p.Thr291Lys	rs6762208	3	185,331,165	<0.001	<0.001	<0.001	<0.001
WFS1	WFS1 p.Val333Ile	rs1801212	4	6,302,519	<0.001	0.001	<0.001	0.004
ANKH	ANKH p.Arg187Gln	rs146886108	5	14,751,305	0.459	0.972	0.447	0.972
POCS	POCS p.His36Arg	rs2307111	5	75,003,678	0.697	0.954	0.702	0.986
PAM-PIIP5K2	PAM p.Asp336Gly	rs35658696	5	102,338,811	0.288	0.885	0.309	0.947
	PIIP5K2 p.Ser1207Gly	rs36046591	5	102,537,285	0.020	0.063		
RREB1 p.Asp1171Asn	RREB1 p.Asp1171Asn	rs9379084	6	7,231,843	0.920	0.997	0.920	0.997
RREB1 p.Ser1499Tyr	RREB1 p.Ser1499Tyr	rs35742417	6	7,247,344	<0.001	0.013	0.005	0.111
LPL	LPL p.Ser474*	rs328	8	19,819,724	0.023	0.832	0.023	0.832
SLC30A8	SLC30A8 p.Arg276Trp	rs13266634	8	118,184,783	0.295	0.823	0.295	0.823
GPSM1	GPSM1 p.Ser391Leu	rs60980157	9	139,235,415	0.031	0.557	0.031	0.557
KCNJ11-ABCC8	KCNJ11 p.Val250Ile	rs5215	11	17,408,630	0.208	0.412	0.481	0.951
	<b>KCNJ11 p.Lys29Glu</b>	<b>rs5219</b>	<b>11</b>	<b>17,409,572</b>	0.190	0.376		
	ABCC8 p.Ala1369Ser	rs757110	11	17,418,477	0.083	0.163		
PLCB3	PLCB3 p.Ser778Leu	rs35169799	11	64,031,241	0.113	0.720	0.130	0.830
TPCN2	TPCN2 p.Val219Ile	rs72928978	11	68,831,364	<0.001	0.004	0.006	0.140
CENTD2	ARAP1 p.Gln802Glu	rs56200889	11	72,408,055	<0.001	<0.001	<0.001	<0.001
KLHDC5	MRPS35 p.Gly43Arg	rs1127787	12	27,867,727	<0.001	<0.001	<0.001	<0.001
WSCD2	WSCD2 p.Thr113Ile	rs3764002	12	108,618,630	0.281	0.955	0.282	0.958
HNF1A p.Ile75Leu	HNF1A Gly226Ala	rs56348580	12	121,432,117	0.358	0.894	0.358	0.894
	<b>HNF1A p.Ile75Leu</b>	<b>rs1169288</b>	<b>12</b>	<b>121,416,650</b>	<0.001	<0.001		
HNF1A p.Ala146Val	HNF1A p.Ala146Val	rs1800574	12	121,416,864	0.269	0.867	0.280	0.902
MPHOSPH9	SBNO1 p.Ser729Asn	rs1060105	12	123,806,219	0.002	0.054	0.002	0.057
ZZEF1	ZZEF1 p.Ile402Val	rs781831	17	3,947,644	<0.001	0.001	<0.001	0.018
MLX	MLX p.Gln139Arg	rs665268	17	40,722,029	0.002	0.038	0.002	0.039
TTLL6	<b>TTLL6 p.Glu712Asp</b>	<b>rs2032844</b>	<b>17</b>	<b>46,847,364</b>	<0.001	<0.001	0.016	0.305
	CALCOCO2 p.Pro347Ala	rs10278	17	46,939,658	0.0100	0.187		
	SNF8 p.Arg155His	rs57901004	17	47,011,897	0.005	0.092		
C17orf58	C17orf58 p.Ile92Val	rs9891146	17	65,988,049	<0.001	0.009	<0.001	0.009
CILP2	<b>TM6SF2 p.Glu167Lys</b>	<b>rs58542926</b>	<b>19</b>	<b>19,379,549</b>	0.211	0.732	0.263	0.913
	<b>TM6SF2 p.Leu156Pro</b>	rs187429064	19	19,380,513	0.049	0.172		
GIPR	GIPR p.Glu318Gln	rs1800437	19	46,181,392	0.169	0.901	0.169	0.901
ZHX3	ZHX3 p.Asn310Ser	rs17265513	20	39,832,628	<0.001	0.003	0.003	0.110
HNF4A	HNF4A p.Thr139Ile	rs1800961	20	43,042,364	1.000	1.000	1.00	1.000
MTMR3-ASCC2	<b>ASCC2 p.Asp407His</b>	<b>rs28265</b>	<b>22</b>	<b>30,200,761</b>	0.011	0.192	0.028	0.481
	ASCC2 p.Pro423Ser	rs36571	22	30,200,713	0.007	0.116		
	ASCC2 p.Val123Ile	rs11549795	22	30,221,120	0.006	0.107		
	MTMR3 p.Asn960Ser	rs41278853	22	30,416,527	0.004	0.065		
PNPLA3	PNPLA3 p.Ile148Met	rs738409	22	44,324,727	0.112	0.691	0.130	0.806
	PARVB p.Trp37Arg	rs1007863	22	44,395,451	0.017	0.103		
PIM3	IL17REL p.Leu333Pro	rs5771069	22	50,435,480	0.041	0.419	0.047	0.475
	IL17REL p.Gly70Arg	rs9617090	22	50,439,194	0.005	0.054		
	<b>PIM3 p.Val300Ala</b>	<b>rs4077129</b>	<b>22</b>	<b>50,356,693</b>	<0.001	0.002		

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975 Chromosome. Pos: Position build 37. PPA: functionally-unweighted prior; aiPPA: annotation informed prior. Index  
976 coding variants are highlighted in bold.

977 **ONLINE METHODS**

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979 **Ethics statement.** All human research was approved by the relevant institutional review  
980 boards, and conducted according to the Declaration of Helsinki. All participants provided  
981 written informed consent.

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983 **Derivation of significance thresholds.** We considered five categories of annotation<sup>16</sup> of  
984 variants on the exome array in order of decreasing effect on biological function: (1) PTVs  
985 (stop-gain and stop-loss, frameshift indel, donor and acceptor splice-site, and initiator codon  
986 variants,  $n_1=8,388$ ); (2) moderate-impact variants (missense, in-frame indel, and splice  
987 region variants,  $n_2=216,114$ ); (3) low-impact variants (synonymous, 3' and 5' UTR, and  
988 upstream and downstream variants,  $n_3=8,829$ ); (4) other variants mapping to DNase I  
989 hypersensitive sites (DHS) in any of 217 cell types<sup>8</sup> (DHS,  $n_4=3,561$ ); and (5) other variants  
990 not mapping to DHS ( $n_5=10,578$ ). To account for the greater prior probability of causality for  
991 variants with greater effect on biological function, we determined a weighted Bonferroni-  
992 corrected significance threshold on the basis of reported enrichment<sup>16</sup>, denoted  $w_i$ , in each  
993 annotation category,  $i$ :  $w_1=165$ ;  $w_2=33$ ;  $w_3=3$ ;  $w_4=1.5$ ;  $w_5=0.5$ . For coding variants  
994 (annotation categories 1 and 2):

995

996 
$$\alpha = \frac{0.05 \sum_{i=1}^2 n_i w_i}{(\sum_{i=1}^2 n_i)(\sum_{i=1}^5 n_i w_i)} = 2.21 \times 10^{-7}.$$

997

998 We note that this threshold is similar to a simple Bonferroni correction for the total number  
999 of coding variants on the array, which would yield:

1000

1001 
$$\alpha = \frac{0.05}{224502} = 2.23 \times 10^{-7}.$$

1002

1003 For non-coding variants (annotation categories 3, 4 and 5) the weighted Bonferroni-  
1004 corrected significance threshold is:

1005

1006 
$$\alpha = \frac{0.05 \sum_{i=3}^5 n_i w_i}{(\sum_{i=3}^5 n_i)(\sum_{i=1}^5 n_i w_i)} = 9.45 \times 10^{-9}.$$

1007 **DISCOVERY: Exome-array study-level analyses.** Within each study, genotype calling and  
1008 quality control were undertaken according to protocols developed by the UK Exome Chip  
1009 Consortium or the CHARGE central calling effort<sup>38</sup> (**Supplementary Table 1**). Within each  
1010 study, variants were then excluded for the following reasons: (i) not mapping to autosomes  
1011 or X chromosome; (ii) multi-allelic and/or insertion-deletion; (iii) monomorphic; (iv) call rate  
1012 <99%; or (v) exact  $p < 10^{-4}$  for deviation from Hardy-Weinberg equilibrium (autosomes only).

1013 We tested association of T2D with each variant in a linear mixed model,  
1014 implemented in RareMetalWorker<sup>17</sup>, using a genetic relationship matrix (GRM) to account  
1015 for population structure and relatedness. For participants from family-based studies, known  
1016 relationships were incorporated directly in the GRM. For founders and participants from  
1017 population-based studies, the GRM was constructed from pair-wise identity by descent  
1018 (IBD) estimates based on LD pruned ( $r^2 < 0.05$ ) autosomal variants with  $MAF \geq 1\%$  (across  
1019 cases and controls combined), after exclusion of those in high LD and complex regions<sup>39,40</sup>,  
1020 and those mapping to established T2D loci. We considered additive, dominant, and  
1021 recessive models for the effect of the minor allele, adjusted for age and sex (where  
1022 appropriate) and additional study-specific covariates (**Supplementary Table 2**). Analyses  
1023 were also performed with and without adjustment for BMI (where available Supplementary  
1024 Table 2).

1025 For single-variant association analyses, variants with minor allele count  $\leq 10$  in cases  
1026 and controls combined were excluded. Association summary statistics for each analysis  
1027 were corrected for residual inflation by means of genomic control<sup>41</sup>, calculated after  
1028 excluding variants mapping to established T2D susceptibility loci. For gene-based analyses,  
1029 we made no variant exclusions on the basis of minor allele count.

1030

1031 **DISCOVERY: Exome-sequence analyses.** We used summary statistics of T2D association  
1032 from analyses conducted on 8,321 T2D cases and 8,421 controls across different ancestries,  
1033 all genotyped using exome sequencing. Details of samples included, sequencing, and quality  
1034 control are described elsewhere<sup>12,15</sup> (<http://www.type2diabetesgenetics.org/>). Samples  
1035 were subdivided into 15 sub-groups according to ancestry and study of origin. Each sub-  
1036 group was analysed independently, with sub-group specific principal components and  
1037 genetic relatedness matrices. Association tests were performed with both a linear mixed  
1038 model, as implemented in EMMAX<sup>42</sup>, using covariates for sequencing batch, and the Firth

1039 test, using covariates for principal components and sequencing batch. Related samples were  
1040 excluded from the Firth analysis but maintained in the linear mixed model analysis. Variants  
1041 were then filtered from each sub-group analysis, according to call rate, differential case-  
1042 control missing-ness, or deviation from Hardy-Weinberg equilibrium (as computed  
1043 separately for each sub-group). Association statistics were then combined via a fixed-effects  
1044 inverse-variance weighted meta-analysis, at both the level of ancestry as well as across all  
1045 samples. P-values were taken from the linear mixed model analysis, while effect sizes  
1046 estimates were taken from the Firth analysis. Analyses were performed with and without  
1047 adjustment for BMI. From exome sequence summary statistics, we extracted variants  
1048 passing quality control and present on the exome array.

1049

1050 **DISCOVERY: GWAS analyses.** The UK Biobank is a large detailed prospective study of more  
1051 than 500,000 participants aged 40-69 years when recruited in 2006-2010<sup>13</sup>. Prevalent T2D  
1052 status was defined using self-reported medical history and medication in UK Biobank  
1053 participants<sup>43</sup>. Participants were genotyped with the UK Biobank Axiom Array or UK BiLEVE  
1054 Axiom Array, and quality control and population structure analyses were performed  
1055 centrally at UK Biobank. We defined a subset of “white European” ancestry samples  
1056 (n=120,286) as those who both self-identified as white British and were confirmed as  
1057 ancestrally “Caucasian” from the first two axes of genetic variation from principal  
1058 components analysis. Imputation was also performed centrally at UK Biobank for the  
1059 autosomes only, up to a merged reference panel from the 1000 Genomes Project (multi-  
1060 ethnic, phase 3, October 2014 release)<sup>44</sup> and the UK10K Project<sup>9</sup>. We used SNPTSTv2.5<sup>45</sup> to  
1061 test for association of T2D with each SNP in a logistic regression framework under an  
1062 additive model, and after adjustment for age, sex, six axes of genetic variation, and  
1063 genotyping array as covariates. Analyses were performed with and without adjustment for  
1064 BMI, after removing related individuals.

1065 GERA is a large multi-ethnic population-based cohort, created for investigating the  
1066 genetic and environmental basis of age-related diseases [dbGaP phs000674.p1]. T2D status  
1067 is based on ICD-9 codes in linked electronic medical health records, with all other  
1068 participants defined as controls. Participants have previously been genotyped using one of  
1069 four custom arrays, which have been designed to maximise coverage of common and low-  
1070 frequency variants in non-Hispanic white, East Asian, African American, and Latino

1071 ethnicities<sup>46,47</sup>. Methods for quality control have been described previously<sup>14</sup>. Each of the  
1072 four genotyping arrays were imputed separately, up to the 1000 Genomes Project reference  
1073 panel (autosomes, phase 3, October 2014 release; X chromosome, phase 1, March 2012  
1074 release) using IMPUTEv2.3<sup>48,49</sup>. We used SNPTESTv2.5<sup>45</sup> to test for association of T2D with  
1075 each SNP in a logistic regression framework under an additive model, and after adjustment  
1076 for sex and nine axes of genetic variation from principal components analysis as covariates.  
1077 BMI was not available for adjustment in GERA.

1078 For UK Biobank and GERA, we extracted variants passing standard imputation quality  
1079 control thresholds (IMPUTE info $\geq$ 0.4)<sup>50</sup> and present on the exome array. Association  
1080 summary statistics under an additive model were corrected for residual inflation by means  
1081 of genomic control<sup>41</sup>, calculated after excluding variants mapping to established T2D  
1082 susceptibility loci: GERA ( $\lambda=1.097$  for BMI unadjusted analysis) and UK Biobank ( $\lambda=1.043$  for  
1083 BMI unadjusted analysis,  $\lambda=1.056$  for BMI adjusted analysis).

1084

1085 **DISCOVERY: Single-variant meta-analysis.** We aggregated association summary statistics  
1086 under an additive model across studies, with and without adjustment for BMI, using  
1087 METAL<sup>51</sup>: (i) effective sample size weighting of Z-scores to obtain *p*-values; and (ii) inverse  
1088 variance weighting of log-odds ratios. For exome-array studies, allelic effect sizes and  
1089 standard errors obtained from the RareMetalWorker linear mixed model were converted to  
1090 the log-odds scale prior to meta-analysis to correct for case-control imbalance<sup>52</sup>.

1091 The European-specific meta-analyses aggregated association summary statistics  
1092 from a total of 48,286 cases and 250,671 controls from: (i) 33 exome-array studies of  
1093 European ancestry; (ii) exome-array sequence from individuals of European ancestry; and  
1094 (iii) GWAS from UK Biobank. Note that non-coding variants represented on the exome array  
1095 were not available in exome sequence. The European-specific meta-analyses were corrected  
1096 for residual inflation by means of genomic control<sup>41</sup>, calculated after excluding variants  
1097 mapping to established T2D susceptibility loci:  $\lambda=1.091$  for BMI unadjusted analysis and  
1098  $\lambda=1.080$  for BMI adjusted analysis.

1099 The trans-ethnic meta-analyses aggregated association summary statistics from a  
1100 total of 81,412 cases and 370,832 controls across all studies (51 exome array studies, exome  
1101 sequence, and GWAS from UK Biobank and GERA), irrespective of ancestry. Note that non-  
1102 coding variants represented on the exome array were not available in exome sequence. The

1103 trans-ethnic meta-analyses were corrected for residual inflation by means of genomic  
1104 control<sup>41</sup>, calculated after excluding variants mapping to established T2D susceptibility loci:  
1105  $\lambda=1.073$  for BMI unadjusted analysis and  $\lambda=1.068$  for BMI adjusted analysis. Heterogeneity  
1106 in allelic effect sizes between exome-array studies contributing to the trans-ethnic meta-  
1107 analysis was assessed by Cochran's  $Q$  statistic<sup>53</sup>.

1108

1109 **DISCOVERY: Detection of distinct association signals.** Conditional analyses were  
1110 undertaken to detect association signals by inclusion of index variants and/or tags for  
1111 previously reported non-coding GWAS lead SNPs as covariates in the regression model at  
1112 the study level. Within each exome-array study, approximate conditional analyses were  
1113 undertaken under a linear mixed model using RareMetal<sup>17</sup>, which uses score statistics and  
1114 the variance-covariance matrix from the RareMetalWorker single-variant analysis to  
1115 estimate the correlation in effect size estimates between variants due to LD. Study-level  
1116 allelic effect sizes and standard errors obtained from the approximate conditional analyses  
1117 were converted to the log-odds scale to correct for case-control imbalance<sup>52</sup>. Within each  
1118 GWAS, exact conditional analyses were performed under a logistic regression model using  
1119 SNPTTESTv2.5<sup>45</sup>. GWAS variants passing standard imputation quality control thresholds  
1120 (IMPUTE info $\geq 0.4$ )<sup>50</sup> and present on the exome array were extracted for meta-analysis.

1121 Association summary statistics were aggregated across studies, with and without  
1122 adjustment for BMI, using METAL<sup>51</sup>: (i) effective sample size weighting of Z-scores to obtain  
1123  $p$ -values; and (ii) inverse variance weighting of log-odds ratios.

1124 We defined novel loci as mapping >500kb from a previously reported lead GWAS  
1125 SNP. We performed conditional analyses where a novel signal mapped close to a known  
1126 GWAS locus, and the lead GWAS SNP at that locus is present (or tagged) on the exome array  
1127 **(Supplementary Table 5)**.

1128

1129 **DISCOVERY: Non-additive association models.** For exome-array studies only, we aggregated  
1130 association summary statistics under recessive and dominant models across studies, with  
1131 and without adjustment for BMI, using METAL<sup>51</sup>: (i) effective sample size weighting of Z-  
1132 scores to obtain  $p$ -values; and (ii) inverse variance weighting of log-odds ratios. Allelic effect  
1133 sizes and standard errors obtained from the RareMetalWorker linear mixed model were  
1134 converted to the log-odds scale prior to meta-analysis to correct for case-control

1135 imbalance<sup>52</sup>. The European-specific meta-analyses aggregated association summary  
1136 statistics from a total of 41,066 cases and 136,024 controls from 33 exome-array studies of  
1137 European ancestry. The European-specific meta-analyses were corrected for residual  
1138 inflation by means of genomic control<sup>41</sup>, calculated after excluding variants mapping to  
1139 established T2D susceptibility loci:  $\lambda=1.076$  and  $\lambda=1.083$  for BMI unadjusted analysis, under  
1140 recessive and dominant models respectively, and  $\lambda=1.081$  and  $\lambda=1.062$  for BMI adjusted  
1141 analysis, under recessive and dominant models respectively. The trans-ethnic meta-analyses  
1142 aggregated association summary statistics from a total of 58,425 cases and 188,032 controls  
1143 across all exome-array studies, irrespective of ancestry. The trans-ethnic meta-analyses  
1144 were corrected for residual inflation by means of genomic control<sup>41</sup>, calculated after  
1145 excluding variants mapping to established T2D susceptibility loci:  $\lambda=1.041$  and  $\lambda=1.071$  for  
1146 BMI unadjusted analysis, under recessive and dominant models respectively, and  $\lambda=1.031$   
1147 and  $\lambda=1.063$  for BMI adjusted analysis, under recessive and dominant models respectively.

1148

1149 **DISCOVERY: Gene-based meta-analyses.** For exome-array studies only, we aggregated  
1150 association summary statistics under an additive model across studies, with and without  
1151 adjustment for BMI, using RareMetal<sup>17</sup>. This approach uses score statistics and the variance-  
1152 covariance matrix from the RareMetalWorker single-variant analysis to estimate the  
1153 correlation in effect size estimates between variants due to LD. We performed gene-based  
1154 analyses using a burden test (assuming all variants have same direction of effect on T2D  
1155 susceptibility) and SKAT (allowing variants to have different directions of effect on T2D  
1156 susceptibility). We used two previously defined filters for annotation and MAF<sup>18</sup> to define  
1157 group files: (i) strict filter, including 44,666 variants; and (ii) broad filter, including all variants  
1158 from the strict filter, and 97,187 additional variants.

1159 We assessed the contribution of each variant to gene-based signals by performing  
1160 approximate conditional analyses. We repeated RareMetal analyses for the gene, excluding  
1161 each variant in turn from the group file, and compared the strength of the association  
1162 signal.

1163

1164 **Fine-mapping of coding variant association signals with T2D susceptibility.** We defined a  
1165 locus as mapping 500kb up- and down-stream of each index coding variant (**Supplementary**  
1166 **Table 5**), excluding the MHC. Our fine-mapping analyses aggregated association summary

1167 statistics from 24 GWAS incorporating 50,160 T2D cases and 465,272 controls of European  
1168 ancestry from the DIAGRAM Consortium (**Supplementary Table 9**). Each GWAS was imputed  
1169 using miniMAC<sup>12</sup> or IMPUTEv2<sup>48,49</sup> up to high-density reference panels: (i) 22 GWAS were  
1170 imputed up to the Haplotype Reference Consortium<sup>20</sup>; (ii) the UK Biobank GWAS was  
1171 imputed to a merged reference panel from the 1000 Genomes Project (multi-ethnic, phase  
1172 3, October 2014 release)<sup>44</sup> and the UK10K Project<sup>9</sup>; and (iii) the deCODE GWAS was imputed  
1173 up to the deCODE Icelandic population-specific reference panel based on whole-genome  
1174 sequence data<sup>19</sup>. Association with T2D susceptibility was tested for each remaining variant  
1175 using logistic regression, adjusting for age, sex, and study-specific covariates, under an  
1176 additive genetic model. Analyses were performed with and without adjustment for BMI. For  
1177 each study, variants with minor allele count<5 (in cases and controls combined) or those  
1178 with imputation quality  $r^2\text{-hat}<0.3$  (miniMAC) or proper-info<0.4 (IMPUTE2) were removed.  
1179 Association summary statistics for each analysis were corrected for residual inflation by  
1180 means of genomic control<sup>41</sup>, calculated after excluding variants mapping to established T2D  
1181 susceptibility loci.

1182         We aggregated association summary statistics across studies, with and without  
1183 adjustment for BMI, in a fixed-effects inverse variance weighted meta-analysis, using  
1184 METAL<sup>51</sup>. The BMI unadjusted meta-analysis was corrected for residual inflation by means of  
1185 genomic control ( $\lambda=1.012$ )<sup>41</sup>, calculated after excluding variants mapping to established T2D  
1186 susceptibility loci. No adjustment was required for BMI adjusted meta-analysis ( $\lambda=0.994$ ).  
1187 From the meta-analysis, variants were extracted that were present on the HRC panel and  
1188 reported in at least 50% of total effective sample size.

1189         We included 37 of the 40 identified coding variants in fine-mapping analyses,  
1190 excluding three that were not amenable to fine-mapping in the GWAS data sets: (i) the locus  
1191 in the major histocompatibility complex because of the extended and complex structure of  
1192 LD across the region, which complicates fine-mapping efforts; (ii) the East Asian specific  
1193 *PAX4* p.Arg190His (rs2233580) signal, since the variant was not present in European  
1194 ancestry GWAS; and (iii) *ZHX3* p.Asn310Ser (rs4077129) because the variant was only  
1195 weakly associated with T2D in the GWAS data sets used for fine-mapping.

1196         To delineate distinct association signals in four regions, we undertook approximate  
1197 conditional analyses, implemented in GCTA<sup>54</sup>, to adjust for the index coding variants and  
1198 non-coding lead GWAS SNPs: (i) *RREB1* p. Asp1171Asn (rs9379084), p.Ser1499Tyr

1199 (rs35742417), and rs9505118; (ii) *HNF1A* p.Ile75Leu (rs1169288) and p.Ala146Val (rs1800574);  
 1200 (iii) *GIPR* p.Glu318Gln (rs1800437) and rs8108269; and (iv) *HNF4A* p.Thr139Ile (rs1800961)  
 1201 and rs4812831. We made use of summary statistics from the fixed-effects meta-analyses  
 1202 (BMI unadjusted for *RREB1*, *HNF1A*, and *HNF4A*, and BMI adjusted for *GIPR* as this signal  
 1203 was only seen in BMI adjusted analysis) and genotype data from 5,000 random individuals  
 1204 of European ancestry from the UK Biobank, as reference for LD between genetic variants  
 1205 across the region.

1206 For each association signal, we first calculated an approximate Bayes' factor<sup>55</sup> in  
 1207 favour of association on the basis of allelic effect sizes and standard errors from the meta-  
 1208 analysis. Specifically, for the  $j$ th variant,

1209

$$1210 \quad \Lambda_j = \sqrt{\frac{V_j}{V_j + \omega}} \exp\left[\frac{\omega \beta_j^2}{2V_j(V_j + \omega)}\right],$$

1211

1212 where  $\beta_j$  and  $V_j$  denote the estimated allelic effect (log-OR) and corresponding variance  
 1213 from the meta-analysis. The parameter  $\omega$  denotes the prior variance in allelic effects, taken  
 1214 here to be 0.04<sup>55</sup>.

1215 We then calculated the posterior probability that the  $j$ th variant drives the  
 1216 association signal, given by

1217

$$1218 \quad \pi_j = \frac{\rho_j \Lambda_j}{\sum_k \rho_k \Lambda_k}.$$

1219

1220 In this expression,  $\rho_j$  denotes the prior probability that the  $j$ th variant drives the association  
 1221 signal, and the summation in the denominator is over all variants across the locus. We  
 1222 considered two prior models: (i) functionally unweighted, for which  $\rho_j = 1$  for all variants;  
 1223 and (ii) annotation informed, for which  $\rho_j$  is determined by the functional severity of the  
 1224 variant. For the annotation informed prior, we considered five categories of variation<sup>16</sup>, such  
 1225 that: (i)  $\rho_j = 165$  for PTVs; (ii)  $\rho_j = 33$  for moderate-impact variants; (iii)  $\rho_j = 3$  for low-impact  
 1226 variants; (iv)  $\rho_j = 1.5$  for other variants mapping to DHS; and (v)  $\rho_j = 0.5$  for all other variants.

1227 For each locus, the 99% credible set<sup>21</sup> under each prior was then constructed by: (i)  
 1228 ranking all variants according to their posterior probability of driving the association signal;

1229 and (ii) including ranked variants until their cumulative posterior probability of driving the  
1230 association attained or exceeded 0.99.

1231

1232 **Functional impact of coding alleles.** We used CADD<sup>34</sup> to obtain scaled Combined Annotation  
1233 Dependent Depletion score (CADD-score) for each of the 40 significantly associated coding  
1234 variants. The CADD method objectively integrates a range of different annotation metrics  
1235 into a single measure (CADD-score), providing an estimate of deleteriousness for all known  
1236 variants and an overall rank for this metric across the genome. We obtained the estimates  
1237 of the intolerance of a gene to harbouring loss-of-function variants (pLI) from the ExAC data  
1238 set<sup>33</sup>. We used the Kolmogorov-Smirnov test to determine whether fine-mapping groups 1  
1239 and 2 have the same statistical distribution for each of these parameters.

1240

1241 **T2D loci and physiological classification.** To explore the different patterns of association  
1242 between T2D and other anthropometric/metabolic/endocrine traits and diseases, we  
1243 performed hierarchical clustering analysis. We obtained association summary statistics for a  
1244 range of metabolic traits and other outcomes for 94 coding and non-coding variants that  
1245 were significantly associated with T2D through collaboration or by querying publically  
1246 available GWAS meta-analysis datasets. The z-score (allelic effect/SE) was aligned to the  
1247 T2D-risk allele. We obtained the distance matrix amongst z-score of the loci/traits using the  
1248 Euclidean measure and performed clustering using the complete agglomeration method.  
1249 Clustering was visualised by constructing a dendrogram and heatmap.

#### 1250 **DATA AVAILABILITY STATEMENT**

1251 Summary level data of the exome-array component of this project can be downloaded from  
1252 the DIAGRAM consortium website <http://diagram-consortium.org/> and Accelerating  
1253 Medicines Partnership T2D portal <http://www.type2diabetesgenetics.org/>.

1254

#### 1255 **MATERIALS & CORRESPONDENCE**

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1257 mark.mccarthy@drl.ox.ac.uk and anubha@well.ox.ac.uk. Reprints and permissions  
1258 information is available at [www.nature.com/reprints](http://www.nature.com/reprints).

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- 1304 **URLs**
- 1305 Type 2 Diabetes Knowledge Portal: <http://www.type2diabetesgenetics.org/>