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The Type 2 Diabetes Knowledge Portal: an open access genetic resource dedicated to type 2 diabetes and related traits

A full list of authors and affiliations appears at the end of the article.

Summary

Associations between human genetic variation and clinical phenotypes have become a foundation of biomedical research. Most repositories of these data seek to be disease-agnostic and therefore lack disease-focused views. The Type 2 Diabetes Knowledge Portal (T2DKP) is a public resource of genetic datasets and genomic annotations dedicated to type 2 diabetes (T2D) and related traits. Here, we seek to make the T2DKP more accessible to prospective users and more useful to existing users. First, we evaluate the T2DKP's comprehensiveness by comparing its datasets to those of other repositories. Second, we describe how researchers unfamiliar with human genetic data can begin using and correctly interpreting them via the T2DKP. Third, we describe how existing users can extend their current workflows to use the full suite of tools offered by the T2DKP. We finally discuss the lessons offered by the T2DKP toward the goal of democratizing access to complex disease genetic results.

Graphical Abstract

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Author Contributions

M.C.C., M.V.G., and J.F. performed investigation and formal analysis; conceptualization was performed by M.C.C., M.V.G., R.K., J.F., K.J.G., M.B., D.J., L.C., B.R.A., M.B., M.C., N.P.B., J.C.F., D.A., P.K., A.C.M., D.S., T.M.K., R.P.W., A.P.B., G.R.A., P.S., T.N.K., L.N., A.P., D.W., N.A.Z., B.A., M.K.T., M.J.B., A.C., A.Y.C., E.B.F., C.S.F., M.R.M., D.F.R., H.R., and M.I.M.; M.C.C. and J.F. wrote the original draft; M.C.C., J.M.M., J.F., M.B., N.P.B., A.C.M., and J.C.F. reviewed and edited the manuscript; M.C.C., R.K., T.N., P.S., P.K., Y.S., Y.J., and A.C.M. performed data curation; P.S., P.D., J.M., D.J., C.G., Q.H., P.S., M.D., A.M., B.R.A., T.G., K.C.H., O.R., P.K., Y.J., R.P.W., A.P.B., S.S., and D.T. developed software; P.D., K.J.G., D.J., B.R.A., P.K., R.P.W., and A.P.B developed visualizations; J.F., K.J.G, M.B., L.C., M.B., A.K., N.P.B, D.S., T.M.K, P.S., T.N.K., L.N., A.P., D.W., N.A.Z, and B.A. performed project administration.

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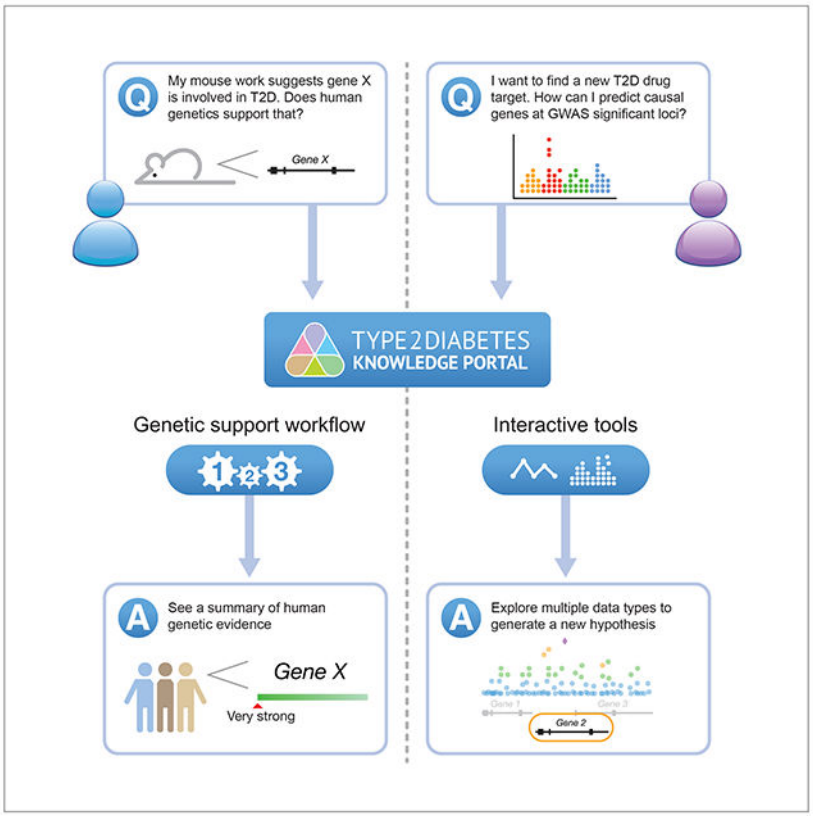

Introduction

Genome wide association studies (GWAS)[1] have elucidated complex trait genetic architectures[2], improved disease risk prediction[3], established causal relationships among traits[4], and identified potential therapeutic targets[5]. Many such insights, however, are not apparent from published results and require downstream analyses of the full set of GWAS associations[6]. These analyses often incorporate auxiliary data to help interpret the molecular and cellular effects of variants within noncoding regions of the genome, which constitute the vast majority of statistically significant associations[7].

Downstream analyses of GWAS results predominantly draw from four types of resource. First, full sets of GWAS summary statistics – that is, *p*-values, allele frequencies, and effect sizes and their standard errors for every variant in a GWAS – are increasingly available for download from consortium websites or other public resources (*e.g.*, the NHGRI-EBI GWAS Catalog[8], GRASP[9], the GWAS Atlas[10], the Global Biobank Engine[11], genebass[12], PheGenI[13], and the IEU OpenGWAS project[14]). Second, genomic annotations – which help interpret variant effects on molecular or cellular processes – include genomic features (*e.g.*, the ENSEMBL[15] and UCSC genome browsers[16]); epigenomic annotations (*e.g.*, from the ENCODE[17] and Roadmap Epigenomics[18] Projects); transcriptomic annotations (*e.g.*, the GEO[19], GTEx[20] portal, or SCAN database[21]); proteomic, protein-protein interaction, and pathway datasets (*e.g.*, UniProt[22], STRING[23], and MSigDB[24]); and perturbational datasets (*e.g.*, the IMPC[25] and MGI[26] databases). Third, many bioinformatic methods integrate

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summary statistics and genomic annotations to draw insights from GWAS associations[6]: some methods have dedicated web portals (*e.g.*, LD Hub[27], MR-Base[28], PredictDB[29]) and some have been integrated within more general "post-GWAS" analysis platforms (*e.g.*, FUMA[30], Open Targets[31]). Fourth, expert knowledge about genetic associations or their biology is often extractable from the literature through manual curation (*e.g.*, OMIM[32], ClinGen[33], HGMD[34]), automated text mining (*e.g.*, PubTator[35], SemMedDB[36]), or a combination of the two (*e.g.*, GWASkb[37]).

Beginning in 2015, we developed the Type 2 Diabetes Knowledge Portal (T2DKP) to address two gaps in the capabilities of these resources from the perspective of type 2 diabetes (T2D) researchers. First, many disease-specific datasets – for example, GWAS of disease-specific endophenotypes[38] or genomic annotations in highly specific cell populations[39] – are too narrow in scope to be identified and included by disease-agnostic resources. Second, many analyses can only be conducted after data from disparate resources are combined – for example, decisions to experimentally characterize variants at a GWAS locus are influenced not only by GWAS association strength but also by genomic annotations of variant regulatory effects and bioinformatic predictions of downstream "effector" genes[40]. The T2DKP addresses these gaps by aggregating and integrating data and methods of many types, while focusing on only one disease area (T2D and related traits).

The T2DKP was the main output of the Accelerating Medicines Partnership® in Type 2 Diabetes (AMP®-T2D), a five-year public-private partnership launched in 2014 to generate, analyze, and "democratize" access to genetic and genomic data for T2D-relevant traits. The ~100 scientists within AMP-T2D – many of whom have led advances in genetic mapping and functional study of T2D over the past two decades[41–43] – have collectively defined the scope and data of the T2DKP and guided its evolution throughout its existence. Initially, the T2DKP provided a simple website to access association statistics from T2D GWAS and whole exome sequencing (WES) studies, and it gradually expanded to include genomic annotations, bioinformatic method results, and data from additional traits. In 2020, the T2DKP saw a major revision to its user interface that created both an opportunity and a challenge with regards to its accessibility. On the one hand, the new interface provides simple visualizations that enable even non-geneticists to incorporate human genetic data into their research – which, if prominent publications are any guide[44], they infrequently do today. On the other hand, the T2DKP's new interface offers an increasingly complex suite of tools that even genetic experts may not know how to fully exploit.

Here we seek to increase the accessibility of the T2DKP to both non-geneticists and genetic experts. We first document the comprehensiveness of the T2DKP by comparing its datasets and genetic associations to those in other major GWAS resources. We then describe the recent expansion of T2DKP data and tools and evaluate – based on an analysis of usage statistics and citations – its current usage patterns. We use these patterns to define two classes of potential T2DKP users and suggest new ways for each to make fuller use of the T2DKP.

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Results

Overview of the T2DKP

The T2DKP contains genetic association summary statistics, genomic annotations, bioinformatic method results, and expert knowledge for T2D and related traits – which include T2D complications (*e.g.*, cardiovascular, hepatic, ocular, and renal traits), glycemic and anthropometric traits, and metabolites (including lipids). Dataset scope is defined by the AMP-T2D consortium, which represents scientists from academia, the pharmaceutical industry, the government, and non-profit organizations[45]. We maintain these datasets through a three-step process (STAR Methods). First, we combine manual and automated approaches to identify datasets of interest, collaborate with the communities that generated each dataset, and aggregate them within the T2DKP "software platform". Second, we subject these datasets to quality control (QC) and automated downstream bioinformatic analyses. In the final step, we communicate results of these analyses through the T2DKP's web-interface and programmatic APIs (Figure 1). At all steps, we ensure that we respect data use restrictions and make only analytical results – and never sensitive individual-level data – publicly available.

The T2DKP web interface includes a set of "core pages" for browsing these results in the vicinity of a gene, variant, or region of interest, and it also offers a suite of more complex tools for expert users (Figure 2). The T2DKP has steadily expanded in its data and functionality over its lifetime, with an accelerating rate of updates since a major redesign in 2020 (Figure 3). This growing complexity and scope of the T2DKP motivates the current article, which is targeted at researchers who may not be fully aware of the T2DKP's capabilities – or who may not know how to use it at all.

Analysis of datasets in the T2DKP

Genetic datasets.—As of October 2022, the T2DKP contained 382 GWAS full summary statistic datasets (Table S1), each consisting of association results (across every SNP in the GWAS) for one or more traits. To evaluate the comprehensiveness of these datasets for T2D and related glycemic traits (fasting glucose (FG), fasting insulin (FI), and HbA1c; Table S2), we compared datasets for these four traits to those within the GWAS Catalog[8], GWAS Atlas[10], and OpenGWAS project[14], three other widely used GWAS association resources (STAR Methods). The T2DKP included 107 datasets across these traits, compared to 155 in the GWAS Catalog, 18 in the GWAS Atlas, and 35 in the OpenGWAS project (Figure 4a). Considering only full summary statistic datasets for these traits (Figure 4b), the T2DKP contained most (107 of 138) of the datasets across the resources, including 71 unavailable elsewhere (Figure 4cd). The 31 summary statistic datasets not included in the T2DKP were either small, old, or largely overlapping with other studies in the T2DKP (Figure 4ef; Table S2). T2DKP datasets skew heavily toward European samples, due to the ethnic and sociodemographic biases of GWAS[46], although ethnic diversity has increased somewhat over time (Figure 4g).

To obtain associations between each variant and each trait in the T2DKP, we employ a "bottom-line" approach (STAR Methods) that meta-analyzes the datasets in which a

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variant is observed and statistically adjusts for the (usually unknown) degree of sample overlap among them[47]. To evaluate the comprehensiveness of both T2DKP bottom-line associations ($p<5\times10^{-8}$ in the meta-analysis) and "dataset-level" associations ($p<5\times10^{-8}$ in one or more datasets), we compared the loci with T2D, FG, FI, or HbA1C associations in the T2DKP to those in the GWAS Catalog and the OpenGWAS project (STAR Methods). As of October 2022, the T2DKP contained 1900 such loci, 1209 (64%) of which were significant at both the dataset-level and in the bottom-line analysis (Figure 5a). Most of the loci unique to the bottom-line analysis had moderate (but not genome-wide significant) evidence of association in multiple datasets (Figure 5b) – such loci are thus only revealed after meta-analysis of T2DKP datasets. Conversely, loci significant only at the dataset-level included those observed only in older or smaller datasets (likely association artifacts) and those unique to an ancestry or analytical approach (true associations, but not significant in the transethnic bottom-line meta-analysis).

Many of these loci (771, 41%) also had associations in the GWAS Catalog, and a smaller number (407, 21%) had associations in the OpenGWAS project. The 1084 loci unique to the T2DKP included 805 loci attributable to T2DKP-exclusive datasets (dataset-level associations in Figure 5d). Conversely, of the 446 loci not in the T2DKP, the majority (364, 81.6%) were due to studies without publicly available association summary statistics (Figure 5e). The other 96 loci were mostly due to old, small, or non-standard studies inconsistent with the larger studies meta-analyzed in the T2DKP (51 out of 96 lead SNPs had $p>0.01$ in the T2DKP bottom line analysis; *e.g.*, Figure 5f). This analysis demonstrates the T2DKP as a comprehensive resource of associations extractable from publicly available summary statistics for T2D and related traits, and the GWAS Catalog as a complementary resource of all published associations (including those from older and smaller studies).

Genomic annotations.—The genetic datasets in the T2DKP are augmented by (as of October 2022) 5,418 genomic annotations, including 304 (5.6%) unique to it (Table S3). The vast majority (5073; 93.6%) of these annotations describe the location of *cis*-regulatory elements (Figure S1a), which include accessible chromatin sites from ATAC-seq or DNase-seq (814, 15.0%), transcription factor binding sites from ChIP-seq (720, 13.3%), and computationally predicted candidate regulatory elements (2504, 46.2%) or chromatin states (1035, 19.1%) from ChIP-seq and DNase-seq. The remaining 345 datasets contain predicted linkages between *cis*-regulatory elements and target genes using data from single-cell co-accessibility (scATAC-seq or snATAC-seq[39]), 3D physical interactions (Hi-C or promoter capture Hi-C), or activity-by-contact (ABC)[48]. These datasets are stored in the Common Metabolic Diseases Genome Atlas (CMDGA)[49], a sister resource connected to the T2DKP through a series of REST APIs.

Each genomic annotation is described with a high-level tissue of origin and a finer-grained biosample (Table S3). As many genomic annotations in the T2DKP are drawn from the ENCODE project[17], the distribution of datasets across tissues is roughly similar to ENCODE. However, because the T2DKP includes additional genomic annotations from T2D-relevant tissues, there are some tissues for which annotations are over-represented relative to ENCODE. For example, as of October 2022, 173 (3.2%) datasets were from whole pancreas or pancreatic islets, compared to 1.5% of datasets in ENCODE for *Homo*

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sapiens cell lines or tissues (fisher p=9.1×10^{-13}). (Figure S1b). Other over-represented tissues included muscle (6.4% in the T2DKP vs. 1.3% in ENCODE; fisher p=6.1×10^{-66}), adipose (1.6% vs. 0.009%; fisher p=2.6×10^{-4}), and kidney (7.4% vs. 3.1%; fisher p=3.8×10^{-32}).

T2DKP usage patterns

To understand T2DKP usage patterns and how we might improve them, we analyzed page accesses (using Google Analytics from October 2021 through March 2022) and the 129 T2DKP citations. Both measures suggest that existing users focus on simple result summaries: 49.3% of page accesses (31,558 out of a total 64,005 accesses) were for the core “region”, “variant”, “gene”, and “phenotype” summary pages (Figure 2), 48.8% of page accesses (31,230) were for informational pages, and only 3.9% of page accesses (1,217) were for more complex tools. Similarly, 81 (86.2%) of the 94 citations used the T2DKP core pages for simple queries.

These usage patterns are consistent with two major categories of current and prospective T2DKP users. First, non-geneticists who primarily work with experimental models likely browse the T2DKP core pages (if they use the site at all[44]) but do not fully understand how to interpret the data within them. Second, researchers who regularly analyze genetic associations likely understand the data on the T2DKP core pages but are mostly unaware of (or do not understand) the more complex tools on the T2DKP – possibly due to the pace with which these tools have been added in recent years (Figure 3). To increase the accessibility of the T2DKP for both non-geneticists and genetic experts, below we describe the T2DKP features most useful to each category of user, along with “best-practices” for their use.

T2DKP usage and best-practices for non-geneticist users

Genetic support workflow.—For non-geneticists, the T2DKP is likely most useful to evaluate “genetic support”[5] for a gene suspected, based on experimental work, to be relevant to disease (Figure 6). Searching a gene name on the T2DKP home page brings the user to the region page, showing genetic associations within 50kb of the gene boundaries. The region page contains a “PheWAS”[50] plot of traits with genome-wide significant associations (filterable to those observed for a chosen ancestry) and (for one or more selected traits) a LocusZoom[51,52] plot or table of associations across the region. Genes with human genetic support usually have at least one associated variant in the region.

A more complete summary of a gene’s genetic support is available on the “gene page”, accessible by clicking a gene symbol at the top of the region page. PheWAS plots and tables show gene-level associations for both common variants (calculated by MAGMA[53] and viewable across ancestries or specific to a chosen ancestry; STAR Methods) and rare variants (optionally viewable for a specific transcript of the gene; STAR Methods) within the T2DKP. Both classes of association are summarized on the gene page by the Human Genetic Evidence (HuGE) Calculator, which implements previously outlined[44] probabilistic calculations of genetic support for a gene.

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If a gene of interest does have genetic support, the "variant page" displays additional provenance underlying each variant association nearby the gene. The variant page contains a PheWAS plot, forest plot, and a table of the bottom-line associations for a variant across traits in the T2DKP. In the table, users can see the dataset-level associations that contributed to the bottom-line analysis for the variant – this feature is useful to evaluate the consistency of the association across studies. All tables and visualizations on the variant page can be filtered to associations specific to a chosen ancestry.

As an example of this "genetic support" workflow, a recent study proposed a novel mode of insulin action based on an interaction between the SIN3A and FOXO1 proteins[54], leading to the hypothesis that selective modulation of FOXO1 could treat hyperglycemia in humans[55]. A researcher wondering whether there is evidence for involvement of *SIN3A* in T2D would enter the gene name on the T2DKP home page to browse the *SIN3A* region page, which indeed shows a T2D GWAS association near the gene (p=9.21×10^{-16}). Browsing further, the *SIN3A* gene page shows that its common variant association for T2D is genome-wide significant (MAGMA p=6.78×10^{-13}) and the HuGE Calculator shows a "Very Strong" level of evidence for association of *SIN3A* with T2D. Similarly, while the region page shows no T2D GWAS association nearby *FOXO1*, the gene page shows a nominally significant (burden test p=0.038) rare variant gene-level association for it, leading to a "Moderate" level of evidence according to the HuGE Calculator. Although neither of these associations unequivocally implicates *SIN3A* or *FOXO1* in T2D, they do add support to the experimental data of the original study[54].

Caveats when using the genetic support workflow.—Several best-practices are important for this "genetic support" workflow. First, while a significant association near a gene supports its involvement in disease, the absence of significant associations does not preclude the gene's involvement in disease – a gene will only produce disease associations if a genetic variant affecting its function is sufficiently frequent in the population. When no associations exist nearby a gene, users can employ the T2DKP PheWAS plots to examine not only the primary trait of interest but also related traits; evaluating associations nearby interacting partners of the gene or for genes within shared pathways can also increase sensitivity in some cases[56]. Second, and conversely, users should not engage in "data dredging"[57] and consider a gene to have support because a single variant nearby it shows association in a single dataset; instead, association evidence for a gene should be considered across all variants, corrected for the number of portal queries (*e.g.*, via Bonferroni correction), and integrated across all datasets – the bottom-line association analysis is our preferred statistical method for evaluating association strength across all T2DKP datasets, but it is an approximation and can also hide population-specific effects or gene-by-environment interactions. The T2DKP HuGE calculator is our preferred tool on the portal to estimate genetic support accounting for these and other caveats, albeit with some simplifying assumptions.

Effector gene lists.—If users would like a list of genes with the strongest genetic support for T2D or related traits, then they should use the "Predicted Effector Genes" tool (STAR Methods). This tool contains four lists of genes predicted (based on different

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methodologies) to mediate GWAS associations in the T2DKP, categorizes genes based on the strength of these predictions, and allows users to see the evidence underlying each prediction. It is useful for analyses of genes identified from unbiased "forward genetic" approaches, such as the construction of potential protein interaction networks for diabetes-related endophenotypes[58].

To illustrate another application of the effector gene list, we investigated the extent to which genes identified from T2D GWAS also harbor rare coding variant associations, of relevance to the debate[59] regarding the ability of GWAS to identify genes central to disease pathogenesis as opposed to genes on the periphery of dense regulatory networks[60]. We downloaded the list of 132 T2D effector genes produced by a curation-based methodology (under the "Curated T2D Effector Gene Predictions" page on the T2DKP "Tools" menu), in which genes are assigned to one of five evidence categories from "Causal" (containing a causal coding variant) to "Weak" (prioritized based on a single line of regulatory or perturbational evidence; STAR Methods). Using a Wilcox test and data from the AMP-T2D-GENES WES study[43] (STAR Methods), we found these genes to be significantly enriched for rare coding variant associations (p=0.015; Figure S2), with this enrichment due mostly to genes in the "Causal" set (p=0.0023 for "Causal" genes, p=0.21 for all other genes). Conversely, the 132 genes with the highest T2D MAGMA scores were not enriched for rare coding variant associations (p=0.27). This example illustrates the intended use of the effector gene list as a more effective starting point (compared to genes simply nearby GWAS associations) for downstream investigation of candidate disease genes.

T2DKP usage and best-practices for genetic expert users

Our usage and citation statistics indicate that most users – even genetic experts – do not routinely use the more advanced T2DKP tools. Many of these tools are complex, and we have therefore developed complete guides for them (Table S4) accessible under the T2DKP "Help" menu. Here, we motivate and provide examples of three advanced analyses that can be conducted with these tools.

Analysis 1: associations across multiple traits.—A variant's or gene's pattern of associations across a range of traits can be useful in basic (*e.g.*, identifying cases of pleiotropy[61]), clinical (*e.g.*, clustering patients into disease subgroups[62]), and translational (*e.g.*, predicting if modulating a candidate drug target will have adverse side effects[63]) research. To visualize a variant's association pattern across traits in the T2DKP, the variant page contains both a PheWAS plot, highlighting association significance and directionality, and a forest plot, highlighting relative effect sizes. Conversely, the "Signal Sifter" identifies association signals following a user-specified association pattern (*i.e.*, positive or negative effects) across a user-specified collection of traits (STAR Methods). For example, we filtered $p<5\times10^{-8}$ fasting insulin associations adjusted for BMI (FIadjBMI) to those matching an "insulin resistance signature" of $p<0.005$ associations with triglyceride levels (TG; same direction of effect as FIadjBMI) and high-density lipoprotein levels (HDL; opposite direction of effect). The resulting 46 associations (Table S5) included 29 previously identified by a 2016 analysis[64], as well as 17 now significant for the insulin resistance signature in larger GWAS conducted since 2016.

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Similar to the Signal Sifter is the "Gene Finder", which identifies genes with a MAGMA *p*-value below a user-specified threshold for each of a user-specified set of traits. For example, the Gene Finder identified 11 genes with $p<2.5\times10^{-6}$ for FIadjBMI, TG, HDL, T2D and Waist-hip ratio adjusted for BMI (Figure 7a). These genes were significantly enriched for expression specific to adipose tissue, a major site of insulin action (subcutaneous adipose tissue-specific expression Wilcox $p=7.8\times10^{-4}$, effect=20.02 "t-stat"[65] units; visceral adipose tissue-specific expression Wilcox $p=1.2\times10^{-3}$, effect=16.1 t-stat units; Figure S2ef; STAR Methods). By comparison, the 11 genes with the lowest T2D MAGMA *p*-values were not as strongly enriched for adipose-specific expression (subcutaneous Wilcox $p=0.045$, effect=4.9 t-stat units; visceral adipose Wilcox $p=0.32$, effect=−0.12 t-stat units; Figure S2gh). These results demonstrate how – through filters on gene-level association *p*-values alone – the Gene Finder can be used as a starting point to prioritize genes that act through a pathway or mechanism of interest.

Caveats for interpreting associations across multiple traits.—As the T2DKP does not yet support formal co-localization analysis[66], a variant associated with multiple traits on the PheWAS plot is not necessarily causal for each trait, and signals identified by the Signal Sifter or Gene Finder may have different causal variants across traits. Genes identified by the Gene Finder are also not necessarily the effector genes for the nearby association signals.

Analysis 2: prioritizing variants at a GWAS locus.—A second advanced use case of the T2DKP is to explore the variants, cell types, regulatory elements, and causal genes underlying GWAS associations[1,67]. The "Variant Sifter" enables users to filter variants within a region based on available credible set(s) and genomic annotations; users can manually select annotations and tissues of interest or use GREGOR enrichments to choose globally disease-relevant annotations (more sophisticated predictions of locus-specific tissues of action[68] are a potential future addition). As one example, a Variant Sifter query of the T2D associations within 50kb of *CDC123* shows 282 variants achieving $p<5\times10^{-8}$, which can be filtered to only one variant (rs11257655) in the most recent credible set[69]. Next, adding genomic annotations for enhancers and transcription factor binding sites, and filtering these to tissues in which each annotation has a GREGOR enrichment of $p<0.05$ and fold-enrichment>2, shows that rs11257655 is contained in a pancreatic enhancer and a pancreatic islet transcription factor binding site in pancreatic islets (Figure 7b). Indeed, rs11257655 has been shown to affect binding of the FOXA1 and FOXA2 transcription factors – which are essential for pancreas and liver development – to an active pancreatic enhancer region[70].

After filtering variants based on credible sets and annotations, the Variant Sifter shows genes linked to any of the remaining variants. For example, the credible sets and genomic annotations nearby *KCNQ1* indicate that rs231361 has a posterior probability of T2D association >0.99 and overlaps accessible chromatin annotations in pancreatic islets (as well as other pancreatic cell types). Viewing genes linked to rs231361 in the pancreas shows connections (via chromatin co-accessibility) to *INS* and *IGF2* – 500kb away – but not *KCNQ1*. Experiments have in fact showed *INS* levels to be affected by genome-editing of rs231361 in stem-cell derived pancreatic beta cells[39].

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Caveats when prioritizing variants at a GWAS locus.—When prioritizing variants with the Variant Sifter, the strongest evidence of causality is a high posterior probability within a credible set (above 80% or even 95%), and presence within a genomic annotation in a disease-relevant tissue provides further[71] – although not conclusive[72] – evidence. Inferences about cell types and genes that mediate an association should be made with care, as genomic annotations are often correlated across tissues, and variants are often linked to multiple genes. Finally, while global enrichments are a useful starting point for selecting genomic annotations, relevant annotations will vary by locus and (ideally) should be chosen based on the pattern of trait associations observed at the locus[62]. Any hypotheses generated from the Variant Sifter should be replicated experimentally.

Analysis 3: interactive coding variant analyses.—A third advanced tool on the T2DKP, the Genetic Association Interactive Tool (GAIT), supports rare coding variant analyses of WES data from the AMP-T2D-GENES[43] (24 traits) and TOPMed[73] (T2D, FG, and FI) studies. Users can select a gene (or transcript), choose among seven pre-defined variant groupings based on functional annotation ("masks")[43], optionally de-select variants from the mask (according to their displayed protein position and bioinformatic annotations), and conduct an on-the-fly aggregate association analysis using one or more methods (a burden test[74], SKAT[75], or SKAT-O[76] analysis; STAR Methods). One use of GAIT is to conduct association analyses of custom collections of coding variants (perhaps those assayed as "functional"[77,78]). Another is to refine association signals to determine the variants most important to the association. For example, a GAIT burden test of *MC4R* variants in AMP-T2D-GENES and the 5/5 mask[43] produces $p=3.2\times10^{-11}$ (odds ratio=1.20) for T2D and $p=9.4\times10^{-3}$ (beta = 0.042 kg/m^2) for BMI, consistent with published results[43]. As previously reported[43], much of this signal is due to the p.I269N *MC4R* variant in the 5/5 mask. With p.I269N excluded, GAIT reports $p=0.018$ (odds ratio=1.12) for T2D and $p=0.90$ (beta=−0.003 kg/m^2) for BMI (Figure 7c). These results suggest that nearly all of the BMI signal for the 5/5 mask – and most but not all of the T2D signal – is due to p.I269N, illustrating how users can dissect the contribution of rare variants to aggregate association signals using GAIT.

Caveats when conducting interactive coding variant analyses.—GAIT is useful primarily for exploratory association analyses where instantaneous results are important. However, it employs a straightforward analysis procedure (STAR Methods) that may not be optimal for all genes or traits. Users should also be careful to correct GAIT *p*-values for the number of analyses they perform. Like those for all T2DKP tools, the results of GAIT should ideally be further investigated or replicated before using them in a publication.

Support for additional analyses.—All T2DKP tools are listed in Table S4. Over time we plan to add additional tools such as analysis of user-specified or predefined pathways[79], automated credible set and co-localization calculations[80], analysis of association heterogeneity across phenotypic subgroups or ancestries (including via random-effects meta-analyses), exploration of richer phenotypes including those measured longitudinally, investigation of genetic or environmental interaction terms[81], and calculations of SNP posterior effect sizes for use in polygenic risk scores or instrumental variable analysis[3].

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For now, users who wish to use T2DKP datasets in such analyses can download many of the original datasets directly from the T2DKP. Processed data can also be accessed programmatically via REST services[82]. In the future we plan to provide additional programmatic access mechanisms, including direct import of T2DKP data into Python or R data structures.

Additional resources

For a more detailed description of T2DKP workflows and visualizations, we have provided several sources of documentation. Links to a step-by-step guide and a tutorial video for the "genetic support" workflow are prominent on the home page and on the pages included within the workflow. These provide a starting point for first-time portal users. Each of the more advanced T2DKP tools has a graphic at the top that illustrates the conceptual steps in the tool, with links shown between each conceptual step and a corresponding user interface component on the page. The graphic contains links to an expanded documentation page and video tutorial for the tool and its underlying data. All portal documentation is organized under its "Help" page, which has sections for Data, Methods, Pages/Tools, and Workflows. Documentation can also be navigated through a full-text search option in the upper right corner of each page.

Discussion

A human genetic association supports a gene's role in disease and increases its viability as a therapeutic target[5]. The T2DKP aims to make such supporting evidence readily available and interpretable in a T2D-specific resource, thereby promoting the understanding and treatment of T2D and its complications. The T2DKP focuses on recent, large, and community-nominated datasets for T2D-related traits and in T2D-relevant tissues, which our analysis suggests form a more comprehensive resource for T2D genetics compared to resources that represent genomic data without regard to a specific disease area. In this article, we have focused on increasing the T2DKP's usability in two respects. First, to increase the reach of the T2DKP to non-geneticists who do not yet incorporate human genetics into their research[44], we have detailed a simple "genetic support" workflow. Second, to inspire expert geneticists to expand their use of the portal to include more complex tools, we have detailed three scientific questions and how they map to tools in the T2DKP. Our hope is that this information will increase both the breadth and the depth of the T2DKP user-base.

Beyond its role as a resource for T2D researchers, the T2DKP provides one potential model for sharing information derived from sensitive datasets in a manner that is broadly accessible but still useful to disease experts. Compared to "data commons"[83] such as the NHLBI BioData Catalyst[84] or the NHGRI AnVIL[85], which provide analytical tools to analyze large or sensitive datasets within a cloud-based workspace, the model of the T2DKP is to delineate individual-level genetic datasets, which in general cannot be made publicly accessible, from summary representations of them, which support the needs of the vast majority of users. This paradigm – in which a public web-interface displays summary statistics automatically calculated from community-maintained private individual-level data

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– could be an effective path to make other types of information in these “data commons” more readily available to users who do not need or desire direct data access.

The T2DKP also suggests a means to encourage researchers to share data and results in settings where they have traditionally been hesitant. It serves as a dedicated portal with community-designed content and branding, providing researchers with an incentive to share data and contribute expertise to manual parts of the data curation process. The data underlying the portal, however, are served through a general and scalable software platform, and improvements in automation of the data discovery process accrue to any other portals built upon the same platform. The potential of “community portals” like the T2DKP has been recognized by other disease communities that have used its platform to build portals for cardiovascular and cerebrovascular disease, type 1 diabetes, and sleep disorders, all of which are now collected with the T2DKP under the broader banner of the Common Metabolic Diseases Knowledge Portal (CMDKP) – the current focus of the AMP-T2D (now AMP®-CMD) partnership following its initial funding period. The growth of these resources illustrates a potentially cost-effective strategy to democratize access to expert-generated genomic data and accelerate the discovery, validation, and interpretation of genetic and genomic results.

Limitations of the study

In the Results section, we have discussed caveats and limitations of key T2DKP workflows and tools. More generally, while the T2DKP aims to be an “authoritative” resource of genetic and genomic data for T2D and related traits, incompleteness and bias in its datasets and functionality are inevitable. We have recently added more automated capture of datasets (STAR Methods), but manual review of datasets has been dominant historically and will remain necessary to some extent in the future. The datasets in the T2DKP are in particular biased toward individuals of European ancestry, as are most GWAS[86], and a major focus in the future will be to address this with studies of more diverse ancestries. Additionally, the T2DKP presents summary association statistics to users, which necessarily discard information available in the original genetic and genomic datasets; in some cases, the summary association statistics have been combined with those of other datasets and therefore may not match those in the original manuscript describing a dataset.

STAR Methods

Resource Availability

Lead contact—Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Dr. Jason Flannick (jason.flannick@childrens.harvard.edu).

Materials Availability—This study did not generate new unique reagents.

Data and Code Availability

- All data reported in this paper are included in the main text, figures, and supplementary files.

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- All original code has been deposited at Zenodo and is publicly available as of the date of publication. DOIs are listed in the key resources table.
- All values used to generate the graphs of the paper can be found in the file Data S1 – Source Data. Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

Method details

GWAS summary statistics—As of October 2022, the T2DKP contained 382 GWAS summary statistic datasets (Table S1), each of which consists of association results (across every SNP in the GWAS) for one or more traits. We identified these GWAS datasets – and regularly identify additional ones to include in the T2DKP – via three mechanisms. First, we monitor the new literature via weekly PubMed searches and by monitoring Twitter to find relevant new preprints and papers. We review these papers to determine whether the summary statistics are publicly available; if they are not, we contact authors to ask whether they would like to contribute their results to the T2DKP. Second, we work with scientists within AMP-T2D and the T2D genetics community to obtain datasets they generate or identify. Often, authors provide a final version of their summary statistics as they prepare their manuscripts, so that the results can be released on the T2DKP immediately upon publication. Third, we work with scientists (funded as part of AMP-T2D) from the European Bioinformatics Institute, home of the GWAS Catalog, to identify new association datasets for T2D-relevant traits for which full summary statistics are available in the GWAS Catalog; we review each of these datasets for eligibility and prioritize those of most interest to the community targeted by the T2DKP. This more automated and systematic data discovery approach complements the other two manual curation approaches that we employ. In these analyses, the standardized ontology terms to which GWAS Catalog traits are mapped are employed to interrogate the Catalog REST-API for traits of relevance to the T2DKP. Datasets for which the specific author-reported trait curated by the GWAS Catalog align to T2DKP traits of interest are then assessed for the availability of full summary statistics and compatibility of the file contents with T2DKP ingest requirements. Finally, datasets are harmonized via the standard pipeline[87] used at the GWAS Catalog before transfer to the T2DKP for loading.

We focus on phenotypes related to T2D, which include T2D complications (*e.g.*, cardiovascular, hepatic, ocular, and renal traits), glycemic and anthropometric traits, and metabolites (including lipids). We prioritize datasets with disease-relevant phenotypes not yet included in the T2DKP, with sample sizes larger than any study yet in the T2DKP, or with subjects of non-European ancestry. While most investigators are enthusiastic about contributing their data to the T2DKP, some have concerns about data sharing or lack resources to do so. To address potential data sharing concerns, we have developed a set of policies (informed by our engagement with these communities over time) for responsible data stewardship[88]. To address potential resource limitations, AMP-T2D has in some cases[38,89] provided funding for investigators to contribute their data.

If a summary statistic dataset is publicly available, we download it and record its original URL for provenance. If the dataset is not publicly available, we obtain it directly from the

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investigators who produced it and record the citation describing it for provenance. We ensure that each summary statistic dataset has for each variant at minimum a chromosome, position, genome build, effect allele, and p-value; we also obtain effect sizes, standard errors, and effect allele frequencies for each variant when available. When a GWAS has calculated credible sets[42], we accept the posterior probabilities of association for each variant. We document the dataset with the genotyping technology used, sample size, and study ancestry. In alignment with the GWAS Catalog, we record study ancestry as one of nine terms: African American or Afro-Caribbean, African unspecified, East Asian, European, Greater Middle Eastern, Hispanic or Latin American, South Asian, Sub-Saharan African, or Mixed Ancestry[90]. We assign ancestry descriptions as they are stated in published papers or in communications with data generators. Due to a lack of reference genetic data for some of these ancestries, in downstream analyses we consider only six ancestries: African American (which includes Sub-Saharan African and African unspecified), East Asian, European (which includes Greater Middle Eastern), Hispanic or Latin American, South Asian, and Mixed Ancestry.

We conduct a four-step QC process for each summary statistic dataset (Figure S3), which are originally provided to the T2DKP in tab delimited format. In the first step, we assign the summary statistic input file standardized column headings and filter out any rows with incompatible chromosomes, reference alleles, or alternate alleles. Additionally, as needed we set optional columns (*e.g.*, odds ratio) to null and infer non-optional columns (*e.g.*, effect size is inferred from odds ratio if it is missing but odds ratio exists). We do not follow any special procedure for different classes of variants; indel variants and SNPs are treated identically. Datasets are also lifted over to GRCh37, if they are specified relative to a different genome build, and assigned identifiers in the format *chromosome:position:reference_allele:other_allele*.

In the second step, we align all effect sizes to the alternate allele (relative to the GRCh37 reference genome). We first analyze strand-unambiguous variants, detecting whether the effect allele (and consequently sign of effect and odds ratio) must be flipped for the non-effect allele to align to the GRCh37 reference genome – we strand-complement reference alleles and alternate alleles if necessary. We then analyze strand-ambiguous variants. We first determine if each variant should be complemented, which we do if (a) >10% of unambiguous variants are complemented, (b) the variant has minor allele frequency (MAF) between 30–70%, and (c) the frequency of the effect allele is further from its frequency in the 1000G project (AF_{1000g}) than it is from 1-AF_{1000g}. After complementing (or not complementing) the variant, we then flip its effect, odds ratio, and effect allele as needed to align the non-effect allele to the GRCh37 reference genome.

The third QC step filters out variants with summary statistics incompatible with the analyses that will be performed on them in subsequent steps of our analysis pipeline. For example, it excludes variants with negative MAF, standard error set to infinity, or odds ratio less than zero.

The fourth and final QC step is effect size scaling for quantitative phenotypes. The scaling process performs linear regression with intercept pinned to zero on $se^2 \sim MAF * (1 - MAF)$

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$*\sqrt{N}$, where *se* is the variant's reported standard error and *N* is its reported sample size. The regression only uses variants with MAF > 0.05 and within the 25%−75% percentiles of standard error. If fewer than 1000 such variants exist, typical for datasets without MAF reported, we instead use a proxy MAF=0.25 for every variant. We divide all variant effects and standard errors by the regression slope if (a) MAF is available and the slope is greater than 2 or less than 0.5 or (b) MAF is unavailable and the slope is greater than 5 or less than 0.2. Otherwise, no scaling is performed.

Whole exome sequencing (WES) summary statistics—As of October 2021, the T2DKP contained associations from two WES datasets: AMP-T2D-GENES[43], containing 45,231 individuals and analyzed for T2D and 24 related quantitative traits, and TOPMed[73], containing associations for T2D, FG, and FI on 23,211 to 44,083 individuals (the TOPMed WES data consist of whole genome sequencing data subset to the exome). For each dataset, the T2DKP includes single-variant association statistics, which we processed following the same procedure that we use for GWAS summary statistics. For the AMP-T2D-GENES dataset, the T2DKP also includes pre-computed gene-level association statistics for seven variant "masks"[43] (annotation categories).

Individual-level genetic data—In addition to datasets with pre-computed GWAS summary statistics, the T2DKP contained (as of October 2022) 38 datasets with individual-level genotypes and phenotypes (Table S1). Most of these datasets include SNP array data from samples measured for T2D-related complications or samples studied longitudinally. Most were collected by researchers in the AMP-T2D consortium and were prioritized to fill gaps in publicly available datasets.

To obtain individual-level datasets for the T2DKP, we collaborate directly with the contributing investigators. After signing a data transfer agreement (DTA), the contributor securely transfers their dataset to one of two sites depending on data use restrictions: the Broad Institute (for datasets allowed to be stored in the United States) or the European Bioinformatics Institute (for datasets required to remain in Europe). Each site stores datasets behind a firewall that prevents public access. We record all phenotypes in a template developed by AMP-T2D to support flexibility in capturing T2D-related traits. Regulations and policies regarding data transfer and appropriate use of the T2DKP are described on an extensive "Policies" page under the T2DKP "Information" menu (https://t2d.hugeamp.org/policies.html).

We then analyze each individual-level dataset using an association analysis pipeline that we developed and used as part of several large-scale T2D association studies[41,43] (Figures S4 and S5). We apply the same pipeline regardless of whether datasets are stored at the Broad Institute or the European Bioinformatics Institute. The pipeline conducts cleaning and normalization of phenotype values, harmonization of genotypes to a modern imputation reference panel[91], sample and variant QC, genetic ancestry and sex determination, measurement and correction for population structure via genetic principal components or genetic relationship matrices, single-variant joint and meta-analysis, and (for WES data) gene-level analysis of various variant masks. In addition to widely used QC techniques (*e.g.*, for sample call rate or variant departures from Hardy-Weinberg equilibrium), our pipeline

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includes a novel sample QC protocol[43] which, for each sample, calculates a series of ~10 metrics indicative of sequencing or genotyping quality (*e.g.*, number of called variants, heterozygosity), adjusts these metrics for ancestry, identifies outlier individuals according to either a single metric or principal components of all metrics, and excludes these individuals from analysis.

We upload the association statistics produced by this pipeline to the T2DKP, following the same procedure as used for pre-computed GWAS summary statistics (Figure S3). We do not upload any individual-level genotypes and phenotypes to the T2DKP.

Genomic annotations—As of October 2022, the T2DKP included 5,418 genomic annotation datasets derived from molecular assays such as RNA-seq, ChIP-seq, ATAC-seq, DNase-seq, and Hi-C of human cell lines, stem cell-derived models, and primary tissue (Table S3). These annotations inform on the location of *cis*-regulatory elements, target genes of these elements, the expression levels of genes, and genetic variant effects on elements and genes (Figure S6). As we do for GWAS datasets, we identify genomic annotation datasets to include in the T2DKP based on the feedback of AMP-T2D scientists and T2DKP users. We focus on genomic annotations derived from tissues most relevant to T2D[92], notably pancreatic islets, all types of adipose tissue, liver, and skeletal muscle. For comparison, we also include annotations derived from other tissues if they are collected and processed via the same methods.

We obtain genomic annotation datasets either by download from public repositories (*e.g.*, GEO, EGA, SRA), download from resources such as ENCODE, or by direct collaboration with a contributing investigator. We assign to each dataset a unique accession number and permanent URL and then document the dataset with metadata describing donor information, cell type or tissue, molecular assay, experimental conditions, protocols, software tools, external references, and publications. We obtain raw experimental assay data (*e.g.*, ATAC-seq, ChIP-seq, Hi-C reads) when available. We standardize cell types and tissue names to the Uber-anatomy ontology for tissues[93], Cell Ontology[94] for cells, and Cell Line Ontology[95] or Experimental Factor Ontology[96] for cell lines. We assign tissues and cells to one of 29 high-level categories describing broad tissue and anatomical system groupings (Table S3). When summary-level annotations derived from these assays (*e.g.*, chromatin state, accessible chromatin sites, target gene predictions) have not been pre-computed, we compute them from the raw data. When summary-level annotations have been pre-computed, we obtain them as well. Prior to including pre-computed annotations in the T2DKP, we perform several QC checks. First, we check the file formats to ensure that they contain the requisite number of fields and the correct type of value per field. Second, we check the contents of pre-computed annotations to ensure that they meet minimum standards such as number of records, distribution of records across the genome, and degree of overlap with blacklisted regions of the genome. While the methods, software tools, and filters used to create pre-computed annotations may in some cases differ from those used to create T2DKP computed annotations, detailed data processing and analysis steps used to create the pre-computed annotations are included as metadata with the annotation record.

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We store all genomic annotation datasets in the Common Metabolic Diseases Genome Atlas[49] (CMDGA), a sister resource to the T2DKP. The CMDGA makes summary-level annotations of each dataset (represented as a set of genomic regions with relevant metadata; *e.g.*, BED files[97]) accessible by the T2DKP software platform through a series of REST APIs. Data that could be subject to data use restrictions (*e.g.*, raw reads) are maintained at the CMDGA and not made available for public access.

Quantification and statistical analysis

Statistical and bioinformatic methods—We process GWAS associations and genomic annotations through a series of five statistical and bioinformatic methods (Figure S7). Each method integrates one or more datasets to make predictions regarding variant associations or their functional effects (*e.g.*, on disease-susceptibility genes, disease-relevant tissues, or regulatory annotations). We select methods to implement based on the following factors (in rough order of priority): ease of implementation, expected impact (based on citations and use of the method), requests by the AMP-T2D and the T2D genetics communities, and requests by users. We apply the methods within an automated analysis pipeline that tracks provenance of the calculations and regularly updates results as new data become available. Wherever possible, we consult and collaborate with the original developers of the methods when encoding them in our analysis pipeline.

The first step in the pipeline is a “bottom-line” association meta-analysis. The goal of this analysis is to calculate an integrated measure of association between each variant in the T2DKP and each trait, accounting for all datasets in which the variant is observed. As many of the larger datasets may have a (usually unknown) degree of sample overlap, the bottom-line analysis statistically infers and adjusts for the degree of overlap[47] by estimating the covariance between effect sizes across studies and then inflating the variance of the test statistic (under the null) to correct for any observed non-zero covariance. This calculation has limitations but offers a compromise between presenting multiple association values for each variant (which are challenging to interpret) and conducting a proper combined analysis of the original genetic data across each study (which is impractical). Because the statistical methodology of the bottom-line method is limited to common (MAF > 5%) variants and a single ancestry, we implement it by first partitioning datasets by ancestry and then separating common and rare variants within each dataset. We next, for each ancestry, (a) conduct an overlap-aware fixed-effect meta-analysis of all common variants across all datasets for the ancestry; (b) assign each rare variant the association statistic from the largest dataset for the ancestry; and (c) combine the common and rare variant associations to produce ancestry-specific bottom-line results. We finally conduct a final fixed-effect meta-analysis (without overlap-detection) of the ancestry-specific results to obtain transethnic association statistics. The assumption of fixed variant effects across ancestries is a simplification and may reduce power to detect ancestry-specific associations; a random-effects meta-analysis is a potential future approach to add to the portal. We retain both the ancestry-level association statistics, and the transethnic association statistics, for downstream analyses.

The second step in the pipeline is to annotate all variants using the Variant Effect Predictor[98] (VEP). We run VEP with its standard command line options and the LofTee and dbNSFP

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plugins, “picking” the annotation in the transcript determined by previously described criteria[43].

Third, we run LD-clumping on the bottom-line associations to produce, for each trait, a set of “clumps”, each consisting of a lead variant and a set of variants in LD with the lead variant. We perform LD-clumping by first running the PLINK[99] clump command with its default parameters. We conduct this analysis separately for each ancestry-level set of associations, estimating LD using an appropriate subset of samples from the 1000G Project; we use African 1000G samples for the African American ancestry, East Asian 1000G samples for the East Asian ancestry, European 1000G samples for the European ancestry, Middle/South American 1000G samples for the Hispanic or Latin American ancestry, and South Asian 1000G samples for the South Asian ancestry. We also conduct a transethnic LD-clumping analysis by clumping the transethnic bottom-line associations five times, once per 1000G ancestry, and then merging clumps across ancestries that have at least one variant in common.

Fourth, for each trait, we calculate the enrichment of each genomic annotation for bottom-line associations. For each trait and each annotation, we apply the GREGOR method[100] to compare the observed proportion of genome-wide significant associations within annotated regions to the expected proportion based on the total size of annotated regions. GREGOR produces a fold-enrichment of each annotation for significant associations, as well as a p-value of statistical significance. We compute these enrichments within each ancestry, using LD estimates from the 1000G project in the same manner as we do for the ancestry-specific clumping analysis. If there does not exist a Mixed Ancestry dataset for the trait that is larger than the combination of the ancestry-level datasets, we then meta-analyze the ancestry-specific enrichments to obtain a transethnic enrichment. If there does exist a larger Mixed Ancestry dataset, then we conduct a GREGOR analysis of the largest Mixed Ancestry dataset to produce a transethnic enrichment; since most GWAS (even those of Mixed Ancestry) are skewed heavily toward European populations, we use LD estimates from the 1000G European samples for this analysis.

Fifth, we calculate gene-level association statistics using MAGMA[53]. We run MAGMA on the bottom-line association results for each trait with its default parameters and a window size of 50kb. We calculate MAGMA associations within each ancestry, as well as at the transethnic level; the choice of samples for LD estimates is analogous to the choice for GREGOR, as is the combination of ancestry-level and Mixed Ancestry datasets to produce transethnic results.

We load the results of these analyses into cloud-based storage buckets (currently housed on Amazon S3) and index them with custom software that we term “BioIndex”[101]. BioIndex uses a MySQL database to map genomic coordinates to storage bucket locations, enabling random access to data for any variant or genomic region directly from cloud storage. Alongside these data we also store references to the original GWAS association statistics (which are also stored in the cloud) or to the original genomic annotations in CMDGA.

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The results of these analyses are integrated into many tools within the T2DKP, and their most significant results for each phenotype are available on the "phenotype page" (Figure 2). All tables and visualizations on the phenotype page can display results calculated across all datasets in the portal or results calculated only for a chosen ancestry.

Pre-computed statistical and bioinformatic method results—In addition to the statistical bioinformatic methods that we automatically apply to every dataset, the T2DKP also includes pre-computed statistical and bioinformatic method results. These include: (a) credible sets (for 40 traits[42,102]); (b) association by contact (ABC) predictions, which integrate ATAC-seq, H3K27ac, and Hi-C data to predict linkages between regions and gene promoters[103]; and (c) predictions of GWAS effector genes (for 11 traits) from a machine learning algorithm[104]. For each pre-computed method result, we record provenance as either a publication or online resource describing the method and data used by it.

Curated knowledge—The T2DKP includes a curated list of putative T2D GWAS effector genes. The goal of this list is to represent the current consensus predictions of the AMP-T2D consortium regarding the genes that mediate T2D GWAS associations, together with the confidence behind each prediction. The effector gene predictions have limitations, as they are based on a series of heuristics rather than a formal statistical methodology. Genes in a region harboring a genome-wide significant T2D association are assigned to one of five tiers (Causal, Strong, Moderate, Possible, Weak) based on three types of evidence: genetic (whether a coding variant in the gene is causal for the association), regulatory (whether genomic annotations support a link between the causal variant and the gene), and perturbational (whether animal or cellular studies of the gene have linked it to T2D or related traits). Each piece of evidence is determined based on a literature review by AMP-T2D scientists, and we record the publication describing it as provenance supporting the effector gene prediction. We note that the effector gene list is unpublished and thus has not undergone peer review, and it is subject to the biases of the scientists who created it; however, it represents (to our knowledge) the best available distillation of curated knowledge regarding T2D effector genes. Over time, as this and other lists are improved, we will update the T2DKP with them and offer users the ability to compare different lists.

In addition to putative T2D effector genes, this gene list also includes putative effector genes for T2D-related diseases and traits. These include genes implicated in monogenic conditions with presentations similar to T2D (*e.g.*, Maturity Onset Diabetes of the Young, Lipodystrophies, or Neonatal Diabetes Mellitus) and putative effector genes for glycemic traits (*e.g.*, fasting glucose or HbA1c).

Tool implementation—To implement the Signal Sifter, we first find all SNPs associated at $p<5\times10^{-8}$ with a lead phenotype and then expand each "index" SNP into a clump using the results of LD clumping. We next filter the clumps to those that contain at least one SNP associated (at a user-specified p-value threshold below 0.05) with each of a set of secondary phenotypes. Next, we set the index SNP for each secondary phenotype to the SNP with the strongest association for that phenotype; the index SNPs may thus differ across phenotypes. Finally, we align the direction of effect for each secondary phenotype index SNP to the direction of effect to the lead phenotype index SNP: we switch the secondary phenotype

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direction of effect for the secondary phenotype index SNP as needed to match secondary phenotype direction of effect for the lead phenotype index SNP.

To implement the Gene Finder, we identify all genes with that have MAGMA *p*-value below a user-specified threshold for each of the selected traits. We sort the resulting list of genes according to the *p*-value produced by a meta-analysis of their trait-level *p*-values (according to Fisher's method).

To implement the Variant Sifter, we identify all variants that are (a) within a user-selected credible set that also (b) overlap any of the user-selected annotations (users can alter this default behavior to retain only variants that overlap all user-selected annotations) and finally (c) are linked to any of the selected genes. We show annotation enrichments as calculated by GREGOR.

To implement the GAIT module for individual-level WES data in the T2DKP (currently the AMP-T2D-GENES and TOPMed WES datasets), we use LDserver[105] to calculate score statistics and covariance matrices[106] from the individual genotypes and phenotypes. LDserver responds to a REST query (specifying a list of variants) from the T2DKP and either computes these statistics on-demand (for the AMP-T2D-GENES dataset) or accesses pre-computed files of genome-wide statistics (for the TOPMed dataset). It then converts these statistics to an aggregate association statistic[106]. Individual-level data stored within LDserver are not directly accessible by the T2DKP.

Analyses conducted for this manuscript—To compare GWAS summary statistic datasets across the T2DKP, GWAS Catalog, OpenGWAS, and GWAS Atlas, we identified the datasets in each resource for T2D, fasting glucose (FG), fasting insulin (FI), or HbA1c. For the T2DKP, we defined these as all datasets listed on the T2DKP "Genetic association datasets" page that included associations for at least one of the four phenotypes. For the GWAS Catalog, OpenGWAS, and GWAS Atlas, we defined these as the datasets listed in the results for searches performed for each of the four phenotypes. We conducted all searches for this analysis on October 16, 2022; the datasets included in our analysis are shown in Table S2. We defined datasets as having "full" summary statistics accessible if either (a) summary statistic files for every variant in the study were available for public download or (b) associations for every variant in the study were represented in the resource through genome-wide query interfaces or genome-wide visualizations (*e.g.*, Manhattan plots on the GWAS Atlas). We defined "partial" datasets as those for which some associations are available, as in the tables of top associations provided by the GWAS Catalog, but for which full summary statistics are not accessible through that resource.

To define associated loci for each trait, we first downloaded association *p*-values from each resource. We then ran a clumping analysis across all associations (using the PLINK 2 software package with parameters –clump-p1 5e-8 –clump-p2 5e-8 –clump-r2 0 –clump-kb 250) to merge genome-wide significant associations within 250kb of each other into clumps (*i.e.*, associated loci). For all calculations comparing the loci included by each resource, we then defined a resource to include a locus if it contained at least one associated variant ($p<5\times10^{-8}$) within the clump.

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To evaluate rare coding variant association enrichments for T2D effector genes, we first downloaded the effector gene list from the T2DKP. Following a previously described procedure[43], we then used a Wilcoxon Rank Sum Test to compare the gene-level association *p*-values from the AMP-T2D-GENES study for these genes to those of a set of genes matched based on various features (such as the number of variants and aggregate allele count within each gene); we removed genes from this analysis which are present on the effector gene list due to rare variant associations (*PAM*, *SLC30A8*, *MC4R*, and *BCL11A*). For comparison, we repeated this analysis for the same number of genes with the lowest MAGMA T2D *p*-values.

To evaluate the enrichment of the set of genes returned by the Gene Finder for adipose-specific expression, we first obtained tissue-specific expression values for each gene across each tissue, based on a previous analysis of samples from the GTEx project[65]. Tissue-specific expression is represented as a "t-stat" for each gene in each tissue. We used a Wilcox test (for each tissue) to compare the t-stat values for genes in the Gene Finder list to the other genes in the genome. For comparison, we also conducted this analysis for the same number of genes with the lowest MAGMA T2D *p*-values.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of interests

A.C. is a Sanofi employee and holds shares and stock options in the company. M.I.M. has served on advisory panels for Pfizer, Novo Nordisk and Zoe Global, has received honoraria from Merck, Pfizer, Novo Nordisk and Eli Lilly, and research funding from Abbvie, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, Pfizer, Roche, Sanofi Aventis, Servier, and Takeda. As of June 2019, M.I.M. is an employee of Genentech, and a holder of Roche stock. M.R.M. is a Pfizer employee and holds shares of stock in the company. M.K.T. is an employee and shareholder of Eli Lilly and Company. As of April 2022, P.D. is an employee and stockholder of Regeneron Pharmaceuticals.

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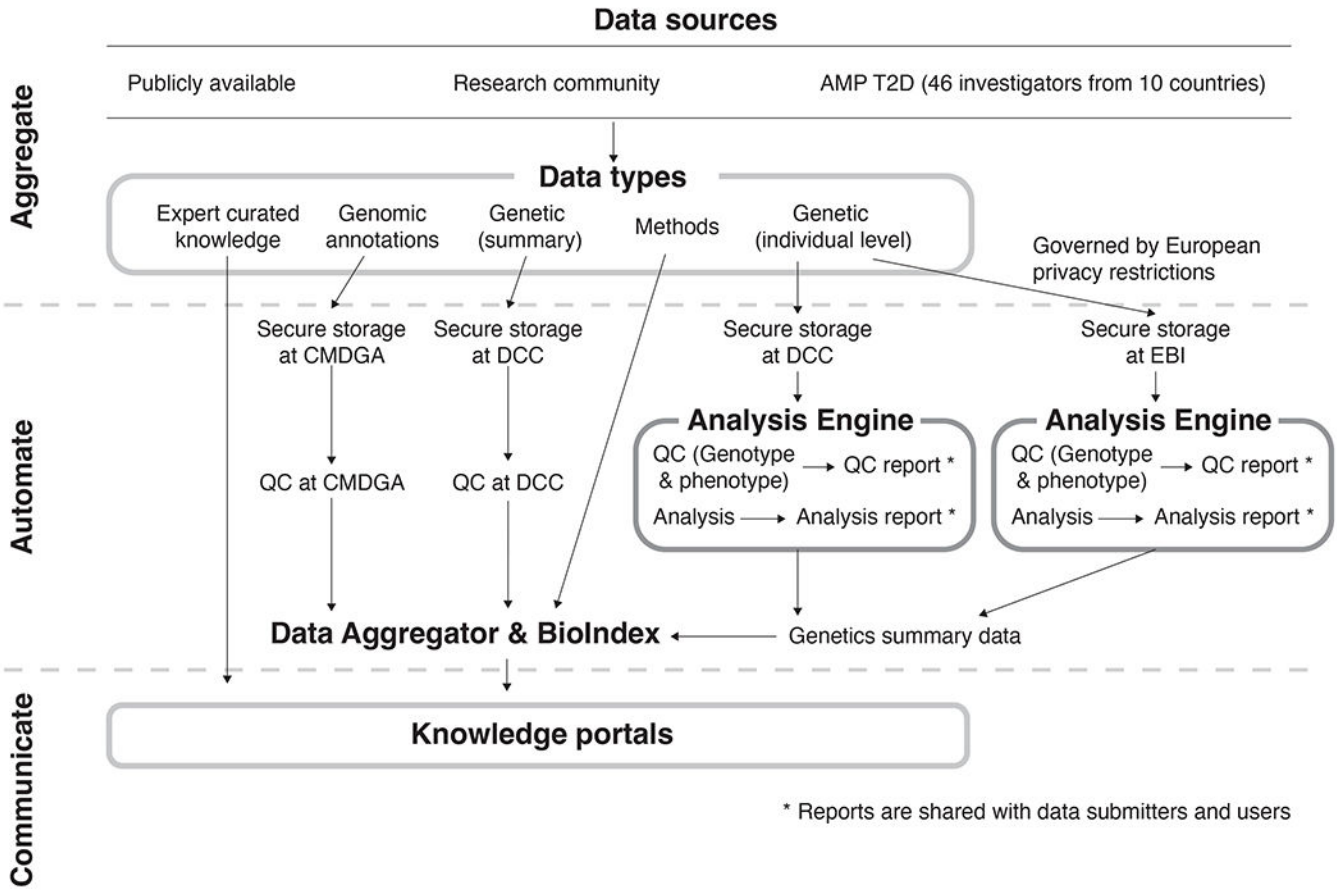

Figure 1: Data are collected, processed by the T2DKP platform, and provided through the T2DKP web-interface via a multi-step process.

Data sources for the T2DKP are of varied origin and of multiple *Data types*. Summary-level genetic datasets are transferred to the Data Coordinating Center (DCC) at the Broad Institute, while genomic annotations are transferred to the Common Metabolic Diseases Genome Atlas (CMDGA). Individual-level genetic datasets are transferred to the DCC or European Bioinformatics Institute (EBI) depending on permissions, and the *Analysis Engine* processes them through a common analytical workflow to produce summary-level associations. The *Data Aggregator* then analyzes summary-level genetic datasets and genomic annotations with a series of bioinformatic methods, the results of which are stored in the *BioIndex*. The *Knowledge portals* access the data within the BioIndex and present them via a web-interface.

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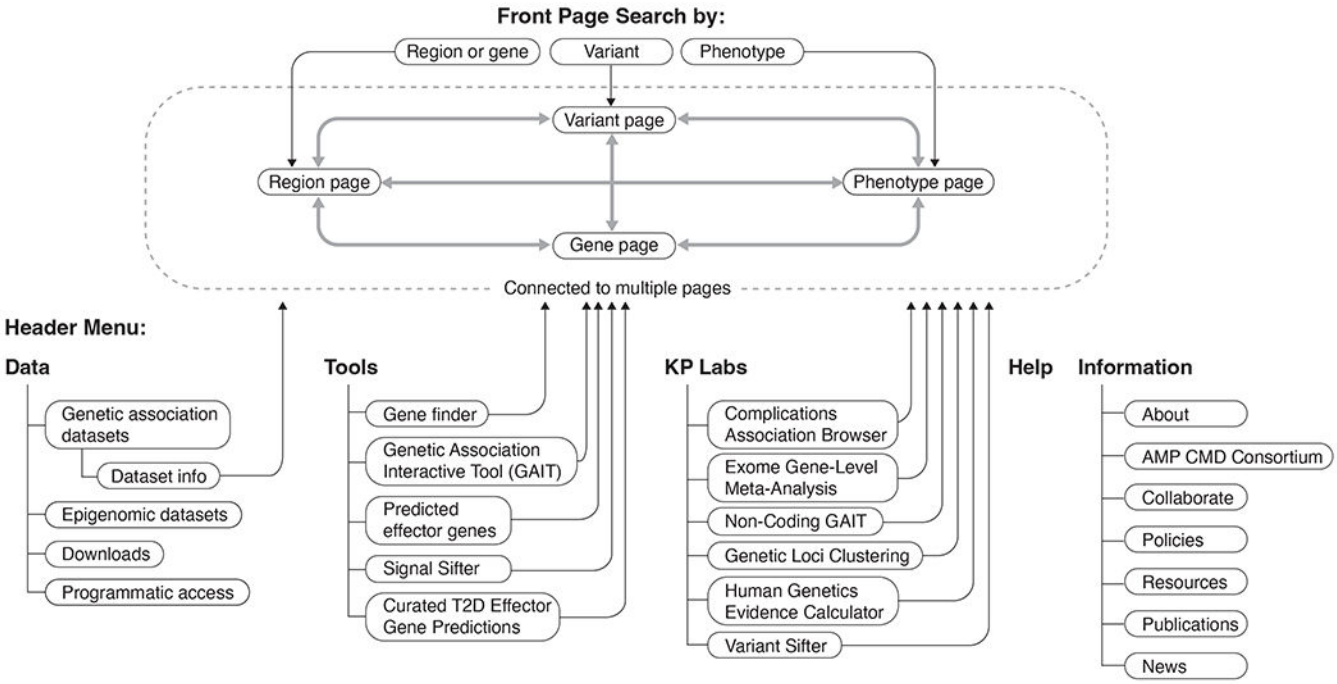

Figure 2: Overview of the T2DKP web-interface.

Users of the T2DKP can browse its data by searching for a phenotype, gene, variant, or region. A phenotype search allows views of all associations and datasets for a trait. A region or gene search directs users to a summary of associations within the region (or nearby the gene). Users can select a gene in the region to navigate to the gene page, which shows a summary of gene-level associations for the gene. The variant page shows a summary of associations for a selected variant. The T2DKP also contains a header menu with information about the data in the resource as well as a suite of tools and visualizations.

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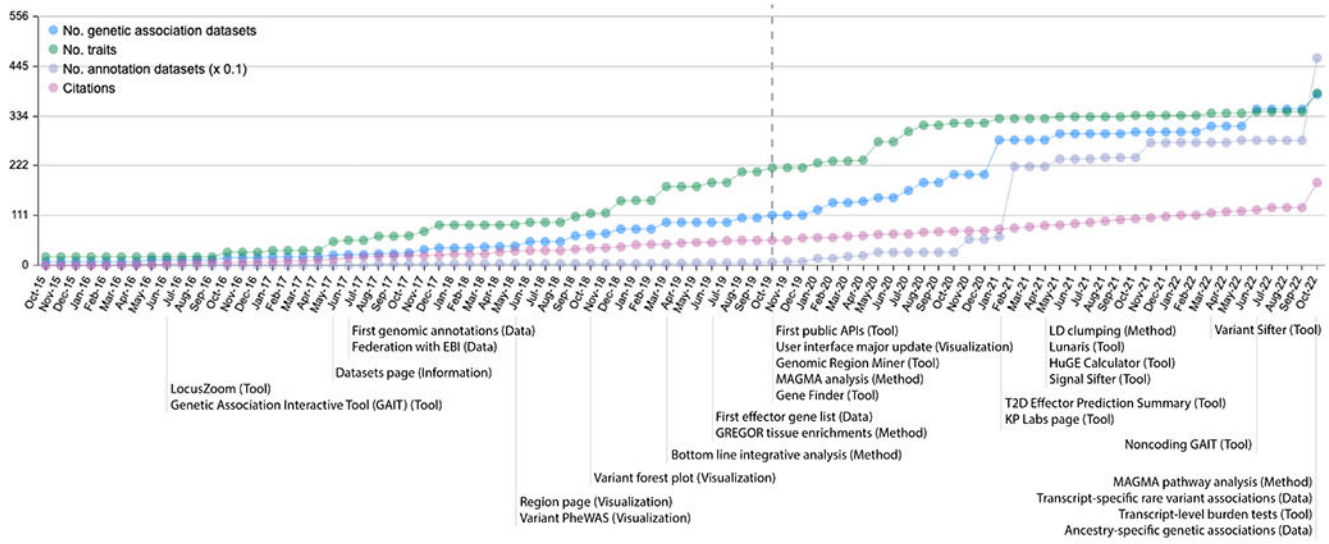

Figure 3: The T2DKP has added datasets and features over time.

On a regular basis, we update the T2DKP with new genetic association datasets (blue dots) for one or more traits (green dots), genomic annotation datasets (purple dots; represented as one-tenth of the actual number), and tools and visualizations (text on bottom of the plot). T2DKP citations (pink dots) have also increased over time. In 2020, the T2DKP received a major update (vertical dashed line) that significantly changed its user interface.

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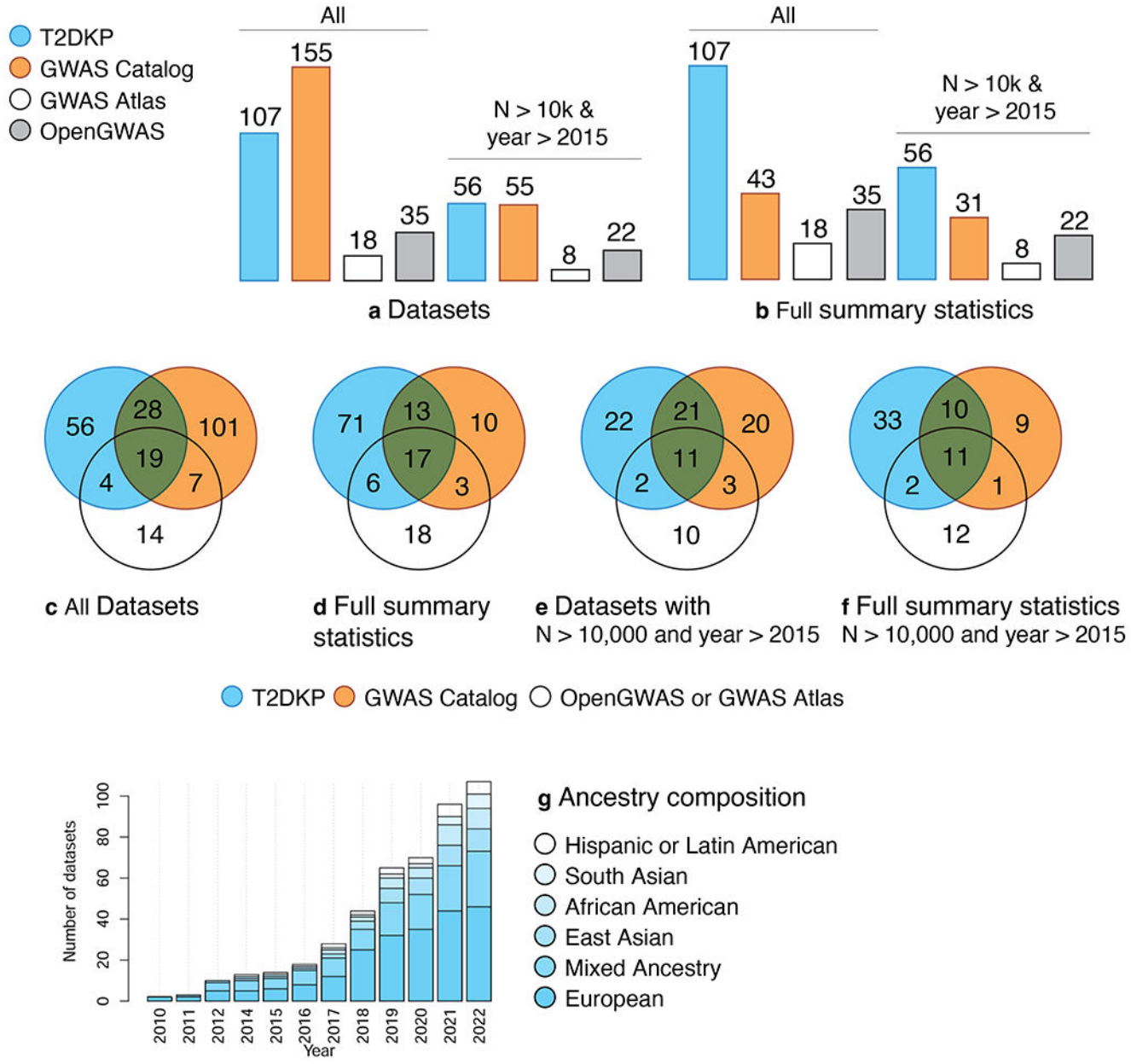

Figure 4: The T2DKP emphasizes genetic datasets for T2D and related traits.

We compared genetic datasets for glycemic traits (T2D, fasting glucose, fasting insulin, and HbA1C) in the T2DKP (blue) to those in the GWAS Catalog (orange), the GWAS Atlas (white), and the OpenGWAS project (gray), in October 2022 (Table S2). We conducted an analysis of all datasets and an analysis of datasets newer than 2015 and with >10K samples. **a.** Considering all datasets in each resource, including those without full summary statistics available, the GWAS Catalog contains the most glycemic trait genetic datasets. **b.** When only datasets with full summary statistics are considered, the T2DKP contains the most glycemic trait genetic datasets. **c.** Both the T2DKP and the GWAS Catalog contain datasets unavailable through other resources. **d.** When only genetic datasets with full summary

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statistics are considered, the T2DKP contains many more datasets unavailable through other resources. **e.** Most of the datasets unique to the GWAS Catalog are either from prior to 2015 or contain fewer than 10K samples. **f.** The T2DKP contains nearly all datasets newer than 2015 and with more than 10K samples. **g.** Datasets in the T2DKP are predominantly from analyses of European samples, but the ethnic diversity it captures has increased over time.

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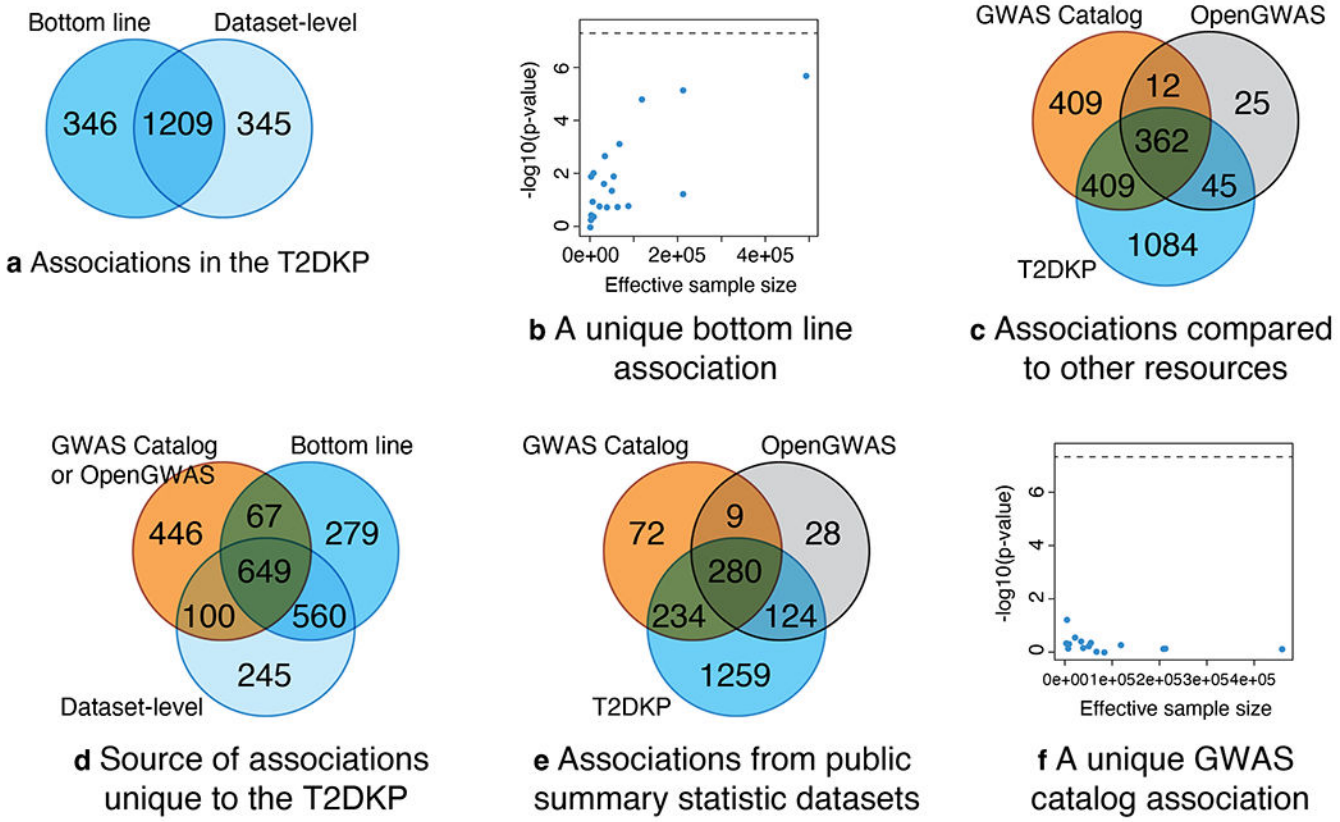

Figure 5: The T2DKP both adds and omits glycemic trait associations relative to the GWAS Catalog.

We evaluated the glycemic trait genetic associations (for T2D, fasting insulin, fasting glucose, and HbA1C) in the T2DKP. We compared genetic associations produced by the T2DKP's overlap-aware meta-analysis (Bottom line, STAR Methods) to genetic associations reported by individual genetic datasets (Dataset-level). **a.** The bottom-line and dataset- level associations largely overlap, but the bottom-line analysis both adds and removes associations. **b.** Associations added by the bottom-line analysis have suggestive associations across many datasets. An example association unique to the bottom-line analysis (rs1000237) has moderate p-values (y-axis) in numerous datasets (points), including nominally significant but not genome-wide significant associations in the datasets with the largest effective sample sizes (x-axis). The horizontal line indicates genome-wide significance. **c.** Comparing the glycemic trait associations in the T2DKP to those in the GWAS Catalog and the OpenGWAS project, each resource contains unique associations. **d**. Associations unique to the T2DKP are a mixture of associations due to datasets unique to it (Dataset-level associations) and its bottom-line analysis (Bottom line). **e.** Most associations unique to the GWAS Catalog are due to studies without summary statistics publicly available. **f.** An example association unique to the GWAS Catalog (rs10932672) is unsupported by larger, more recent datasets in the T2DKP (points on the right side of the plot).

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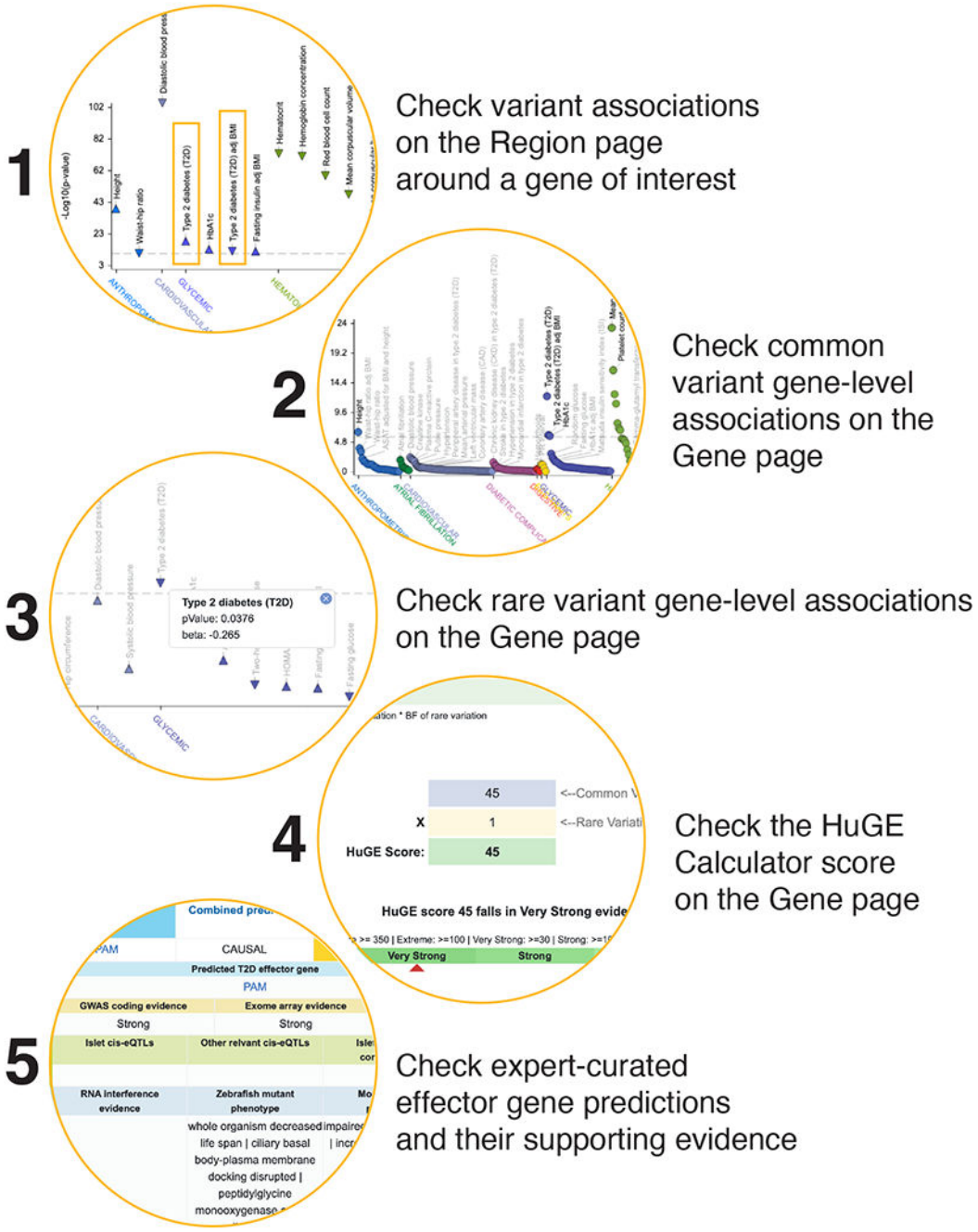

Figure 6: We recommend non-geneticists follow a "genetic support" workflow within the T2DKP.

To evaluate whether human genetic associations support the involvement of a gene of interest in human disease, users can first use the "region page" to see if the gene lies nearby associations (1), then use the "gene page" to view a distillation of these associations into a gene-level score (2) and also view complementary rare variant associations for the gene (3). The HuGE calculator, also on the gene page, summarizes these two gene-level associations into a single score for the gene (4). The T2DKP effector gene list contains a curated set of

genes suggested from genome-wide analyses to be involved in disease (5). Table S4 contains information on these and other modules of the T2DKP.

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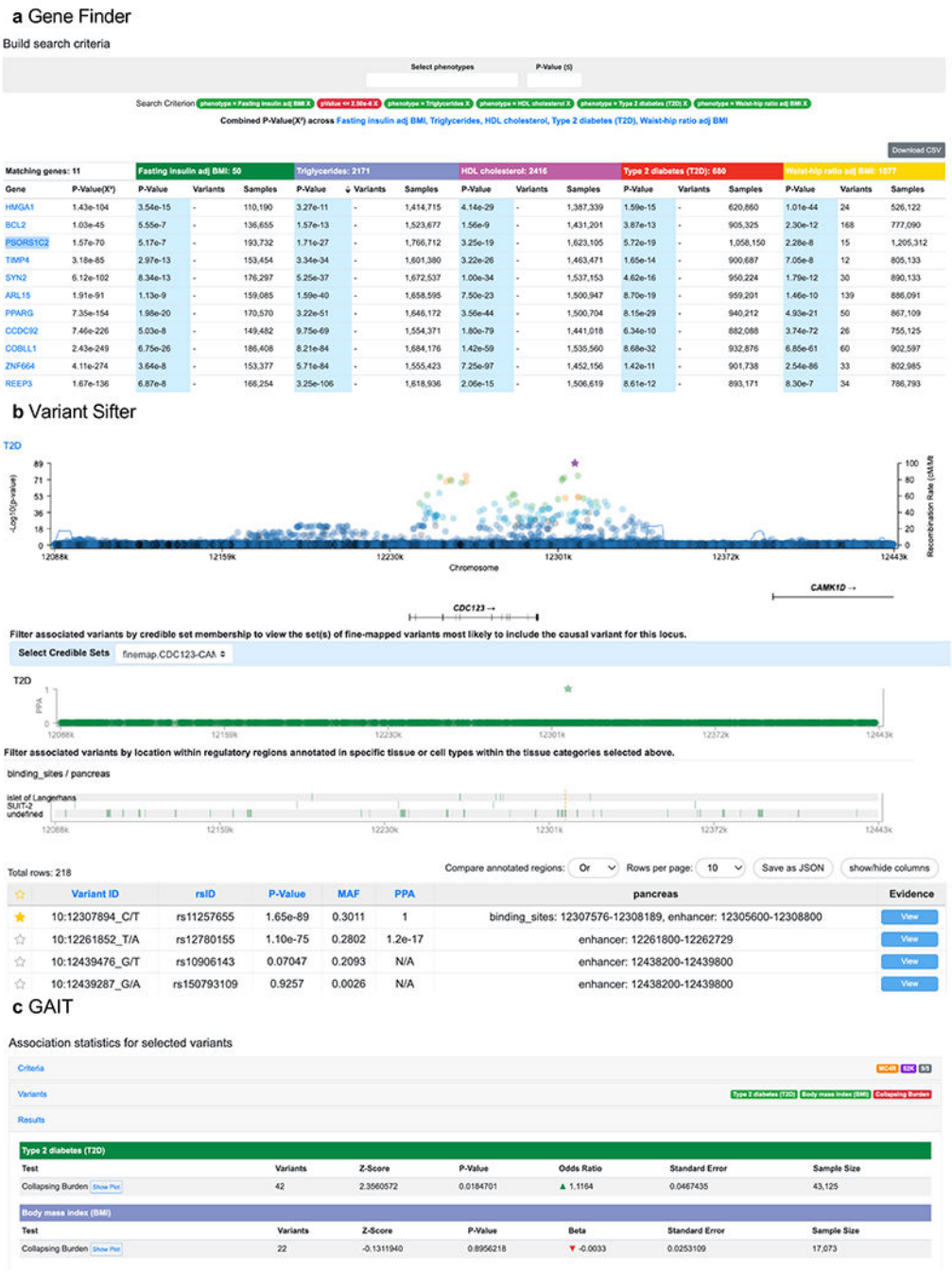

Figure 7: The T2DKP enables exploratory and interactive analyses for the genetic expert user.

a. A Gene Finder search for genes associated with Fasting Insulin adjusted for BMI, Triglycerides, HDL cholesterol, T2D, and Waist-hip ratio adjusted for BMI returns 11 genes that have MAGMA $p<2.5\times10^{-6}$ for each trait. These genes were significantly enriched for adipose tissue-specific expression (Figure S2ef) **b.** A query of '*CDC123*' on the Variant Sifter shows a regional plot of the T2D association. Tracks below the plot show the locations of variants in the credible set and genomic annotations for transcription factor binding sites within the pancreas. A table lists the variants within the credible set that overlap the

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displayed genomic annotations. The actual Variant Sifter page contains more visualizations than those shown in the figure; because of space limitations we have spliced the LocusZoom plot, credible sets plot, annotations plot, and variant table together. **c.** An association analysis in GAIT between rare *MC4R* variants (in the 5/5 mask) and T2D shows the impact of p.I269N on the association signal – after removing the variant from the analysis, the T2D association p-value is increased by nine orders of magnitude and the BMI association is ablated. Table S4 contains information on these and other modules of the T2DKP.