Psoriasis and type 2 diabetes (T2D) are complex conditions with significant impacts on health. Patients with psoriasis have a higher risk of T2D (~1.5 OR) and vice versa, controlling for body mass index; yet, there has been a limited study comparing their genetic architecture. We hypothesized that there are shared genetic components between psoriasis and T2D. Trans-disease meta-analysis was applied to 8,016,731 well-imputed components between psoriasis and T2D. Trans-disease meta-analysis further revealed four genome-wide significant loci (P < 5 × 10^{-8}) with evidence of colocalization and shared directions of effect between psoriasis and T2D not present in body mass index. The proteins coded by genes in these loci (ACTR2, ERL1N, TRMT112, and BECNT) are connected through NF-kB signaling. Our results provide insight into the immunological components that connect immune-mediated skin conditions and metabolic diseases, independent of confounding factors.

INTRODUCTION
Psoriasis is a complex skin disease, which affects over 7 million adults in the United States (Rachakonda et al., 2014), causing painful lesions and itching. Furthermore, psoriasis comorbidities account for more than half of the direct healthcare costs (Brezninski et al., 2015; Feldman et al., 2017; Pilon et al., 2019; Vanderpuye-Orgele et al., 2015). Diabetes, the seventh leading cause of death in the United States (posing an economic burden of over $300 billion per year [American Diabetes Association, 2018]), was to our knowledge among the first psoriasis comorbidities identified (Strauss, 1897; Takeshita et al., 2017). Epidemiological studies show that type 2 diabetes (T2D) and psoriasis are significantly associated, with reported ORs of ~1.5 (Dubreuil et al., 2014; Hemminki et al., 2015) after controlling for body mass index (BMI) and other covariates. Patients with psoriasis exhibit a reduced incretin effect (Gyldenløve et al., 2015) and insulin secretion in response to oral glucose, which is considered to be indicative of pre-diabetes. Notably, patients with higher severity of psoriasis (i.e., more extensive skin involvement) were found to be at a greater risk of developing T2D (Wan et al., 2018).

The high incidence of specific comorbidities for patients with chronic diseases (Ellinghaus et al., 2016; Hu et al., 2016; Meghani et al., 2013; Pefoyo et al., 2015) suggests potential genetic relationships among these conditions. Whereas large-scale GWASs have been conducted to reveal disease susceptibility loci for psoriasis (Patrick et al., 2018; Tsoi et al., 2017) and T2D (Mahajan et al., 2018) separately, so far, there has been a very limited study into the shared genetic signals between these conditions. Wang et al. (2017) genotyped the lead markers for 51 T2D loci in psoriasis cases and controls and found two (in proximity to ST6GAL1 and JAZF1, respectively) to be significantly associated with psoriasis among the Chinese population. However, no other Chinese studies of psoriasis have replicated these loci, and we were unable to replicate the associations (even at nominal significance) in our own Caucasian cohorts (Patrick et al., 2018; Tsoi et al., 2017). Another study (Quaranta et al.,
2009) explored T2D and psoriasis signals in proximity to CDKAL1 for Caucasian patients but concluded that despite their close location, the association signals were completely independent ($r^2 = 0.04$). However, these previous studies may be limited by their candidate gene approach and by not considering potential confounding factors such as BMI. More broadly, psoriasis and T2D are similarly mediated by T helper type 1 signaling as well as by cytokines TNF and IL-6, with further possible links, including leptin, adiponectin, VEGF, and IGF-II (Davidovici et al., 2010). These shared molecular pathways merit further attention as potential contributors to genetic similarities between the diseases.

By conducting a trans-disease meta-analysis (TDMA) of nearly 1 million individuals from GWAS of previously established consortia for the two diseases, our aim was to assess the genetic similarities between T2D and psoriasis to help us understand the molecular mechanisms these conditions have in common. In addition to revealing four shared loci between psoriasis and T2D, we used Mendelian randomization (MR) to unravel the causal relationships and identified the putative mechanisms involving TNF receptor–associated factor TRAF6 that may explain these connections. Ultimately, our findings enhance our understanding of genetic risk factors and their associated pathways, thus improving precision health care for individuals suffering from psoriasis and/or T2D.

RESULTS
We performed TDMA (Figure 1a) between psoriasis (11,024 cases and 16,336 controls from our recent meta-analysis [Patrick et al., 2018]) and T2D adjusted for BMI (74,124 cases and 16,336 controls from our recent meta-analysis). We then performed multivariable MR, with BMI summary statistics from 806,834 samples in the Genetic Investigation of ANthropometric Traits consortium as a co–summary statistics from 806,834 samples in the Genetic Investigation of ANthropometric Traits consortium (Pulit et al., 2019), and the 59 other previously reported loci for psoriasis ([Patrick et al., 2018]) and T2D (Mahajan et al., 2018; Tsoi et al., 2017); however, the chromosome 2 locus (2p14) is, to our knowledge, a previously unreported GWS signal for psoriasis ($P = 6.6 \times 10^{-5}$ in psoriasis meta-analysis) as is the chromosome 11 locus (11q13.1) for T2D ($P = 7.8 \times 10^{-5}$ in T2D meta-analysis).

Functional interpretation of shared loci
To investigate which cell types are affected by the shared psoriasis and T2D genetic signals, we applied GARFIELD (lotchkova et al., 2019) to evaluate the overlap between different chromatin marks with the linkage disequilibrium (LD)–independent significant markers in the TDMA (analysis restricted to markers more significant in TDMA than in both individual diseases). We first studied the enrichment across 1,005 different features representing cell types and annotation marks. Strong enrichment was observed in blood tissue (Supplementary Figure S3), with 48 of 60 (80%) DNase-sequencing experiments having their hypersensitive sites significantly overlapping with disease-shared loci after Bonferroni correction (i.e., $P < 9.7 \times 10^{-5}$), indicating potential immune-cell involvement.

We repeated the enrichment analysis after excluding the major histocompatibility complex region and found that blood was still the most enriched tissue (Figure 2a), with four of the top five most significantly enriched features pertaining to GM12878 lymphoblastoid cells (Supplementary Table S3). We acknowledge that GM12878 possesses more epigenomic data than other immune cells; however, it allows us to highlight the involvement of the regulatory mechanisms in immune cells in general. We then applied GARFIELD to active regulatory elements measured by histone H3 lysine 27 acetylation marks in different immune cells (Farh et al., 2015). Interestingly, T helper type 17 cells were now the most significant ($P = 4.8 \times 10^{-8}$), overlapping in particular our chromosomes 10 and 17 loci, and other immune-cell types were also more enriched (Figure 2b) than

significant in each disease meta-analysis ($P = 1.6 \times 10^{-6}$ for psoriasis and $P = 7.1 \times 10^{-7}$ for T2D) but was GWS ($P = 1.0 \times 10^{-9}$) in TDMA. This locus is of particular interest because the lead trans-disease marker (rs12265333) was the top signal for psoriasis and the third most significant signal for T2D in the individual disease association studies. Crucially, only one of the loci identified by our approach (chromosome 11, TRMT112) was significantly associated with BMI in summary statistics from the Genetic Investigation of ANthropometric Traits consortium (Pulit et al., 2019), and the effect of the BMI signal was in the opposite direction to that of the psoriasis and T2D signal, suggesting that they are not on the same haplotype.

In the Michigan Genomics Initiative (MGI) data, the risk allele frequencies (RAFs) for the lead marker at each of the four loci were higher (8% on average) for patients with both diseases than for controls (Table 2). Interestingly, for all but the 2p14 loci, the RAF was higher for controls than for patients with only one of the diseases, suggesting that our TDMA approach performed as intended by selecting association signals driven by a shared mechanism rather than being dominated by one or the other disease. The four shared loci are all in proximity to known signals for psoriasis and/or T2D (Mahajan et al., 2018; Tsoi et al., 2017); however, the chromosome 2 locus (2p14) is, to our knowledge, a previously unreported GWS signal for psoriasis ($P = 6.6 \times 10^{-5}$ in psoriasis meta-analysis) as is the chromosome 11 locus (11q13.1) for T2D ($P = 7.8 \times 10^{-5}$ in T2D meta-analysis).
lymphoblastoids in GARFIELD’s default annotation set. These results illustrate specific immune-cell involvement shared between the diseases, with T helper type 17 cells playing a key role in the development of psoriasis (Di Cesare et al., 2009) and suggesting involvement in T2D (Ip et al., 2016).

Three of the four genetic signals identified by our approach carry missense mutations: the chromosome 17 lead marker is a missense variant for \( TUBG2 \), the chromosome 11 lead marker is a missense variant for \( CCDC88B \), and the chromosome 10 lead marker is in high LD \( (r^2 = 0.94) \) with a missense variant for \( CHUK \). However, Sorting Intolerant From Tolerant (Kumar et al., 2009) and Polymorphism Phenotyping, version 2 (Adzhubei et al., 2013) suggest that these mutations are unlikely to have a strong deleterious effect on protein function.

Therefore, instead of focusing on the best signal in the TDMA, we broadened our investigation to the Bayesian credible sets for each locus for their potential biological effect. Interestingly, the 95% Bayesian credible sets contained fewer markers for TDMA than for either of the individual traits at three of the four loci (Supplementary Table S4). We then recorded the Combined Annotation Dependent Depletion score for each marker in the intersection of the credible sets (Rentzsch et al., 2019) (TDMA and/or psoriasis and/or T2D) for each locus (Supplementary Table S5) and identified all their significant cis-expression quantitative trait loci (eQTL) gene targets (false discovery rate \(< 0.05\) ) in three different eQTL datasets for blood (Jansen et al., 2017; Võsa et al., 2018; Westra et al., 2013). The PHRED-scaled Combined Annotation Dependent Depletion score for six of the

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Figure 1. TDMA. (a) Vertical Manhattan plots of the meta-analysis association results for psoriasis and T2D, showing GWS \((P \leq 5 \times 10^{-8})\) markers in red and shared loci identified by our TDMA in blue. (b) Regional association plots for the chr10 locus in psoriasis and T2D (with the lead marker in purple). The locus is suggestively significant for each disease and GWS in the TDMA. Chr, chromosome; GWS, genome-wide significant; STAT, signal transducer and activator of transcription; T2D, type 2 diabetes; TDMA, trans-disease meta-analysis.

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<table>
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<tr>
<th>Marker ID</th>
<th>Minor Allele Frequencies</th>
<th>Meta-Analysis ORs (both)</th>
<th>ID Chr</th>
<th>Nearest Gene</th>
<th>Position (hg19)</th>
<th>Nearest-by-GWAS BMI (both)</th>
<th>Type of Analysis</th>
<th>Annotation Dependent Depletion score</th>
<th>Comb Annotation Dependent Depletion score</th>
<th>Combined Annotation Dependent Depletion score</th>
<th>PHRED-scaled Combined Annotation Dependent Depletion score</th>
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<th>Nearest Gene</th>
<th>Position (hg19)</th>
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<th>Type of Analysis</th>
<th>Annotation Dependent Depletion score</th>
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Abbreviations: BMI, body mass index; Chr, chromosome; DIAGRAM, DIAbetes Genetics Replication And Meta-analysis; GIANT, Genetic Investigation of ANthropometric Traits; GWS, genome-wide significant; ID, identification document; STAT, signal transducer and activator of transcription; T2D, type 2 diabetes; TDMA, trans-disease meta-analysis.

Markers (in chromosomes 2 and 10) was higher than 10.0, indicating that they are within the top 10% most deleterious variants in the genome, and for one marker (the missense variant rs2230804 in chromosome 10), the score was 21.4, indicating that it is in the top 1%. According to the three blood eQTL databases, the expression of 34 genes in the blood is associated with at least one marker in the intersection of the credible sets, with capture Hi-C results showing contacts between the promoters for many of these genes and the credible set markers in lymphoblastoid cells, pancreas, adipose, liver, skeletal muscle, thymus, and keratinocytes (Supplementary Table S6). Significantly, the PHRED-scaled Combined Annotation Dependent Depletion score for the most significant eQTL of each gene (mean = 7.1; SD = 2.6) was significantly higher (Wilcoxon rank-sum test $P = 2.76 \times 10^{-5}$) than that of the full set of intersected markers (mean = 5.5; SD = 4.5). Furthermore, all but two of the genes (GPR137 and TRPT1) we identified using the eQTLGen database (94%) have higher mean PHRED-scaled Combined Annotation Dependent Depletion score for eQTLs in the intersection of the credible sets than for the full set of eQTLs for each gene from the database (Supplementary Table S7), suggesting that the markers identified by our approach are more likely to have a larger biological effect.

Interestingly, four proteins encoded by genes from each of the four loci (ACTR2, ERLIN1, TRMT112, and BECN1) are presented in a protein–protein interaction dataset (Chen et al., 2012) to interact with the hub protein TRAF6 (enrichment $P = 1.3 \times 10^{-6}$). TRAF6 mediates NF-kB expression and has previously been implicated in the development of both psoriasis (Hüffmeier et al., 2010) and T2D (Balasubramanyam et al., 2011). ACTR2 ($P = 5.0 \times 10^{-18}$, fold change = 1.85) and TRMT112 ($P = 5.4 \times 10^{-13}$, fold change = 1.57) were found to be upregulated in microarray expression (Gudjonsson et al., 2009) and RNA sequencing (Tsai et al., 2019) data from the GIANT consortium meta-analysis, respectively (Supplementary Table S8), for lesional psoriatic skin compared with that for healthy skin. ACTR2 was also upregulated in the skeletal muscle (Wu et al., 2007) ($P = 8.7 \times 10^{-12}$, fold change = 1.76) and the subcutaneous adipose tissue (Soronen et al., 2012) ($P = 2.4 \times 10^{-2}$, fold change = 1.58) from patients with T2D compared with that from healthy controls but downregulated in the pancreas (Dominguez et al., 2011) ($P = 1.6 \times 10^{-2}$, fold change = 0.31). Similarly, BECN1 was upregulated in the skeletal muscle ($P = 5.4 \times 10^{-7}$, fold change = 1.70) and downregulated in the pancreas ($P = 3.3 \times 10^{-2}$, fold change = 0.48), and both TRMT112 ($P = 4.8 \times 10^{-3}$, fold change = 0.63) and ERLIN1 ($P = 2.7 \times 10^{-3}$, fold change = 0.57) were downregulated in the pancreas of patients with T2D compared with that of healthy controls.

**MR to infer causal relationship**

We next evaluated whether there is a causal relationship between psoriasis and T2D after taking into account the effect of BMI. Rather than disease incidence (which can be heavily affected by confounders), MR uses genetic markers associated with functions or traits of interest to model the effect of one or more exposures on the outcome. We used genetic associations for BMI from 806,834 samples in the
DISCUSSION

The relationship between immune-mediated skin diseases and metabolic disorders is highly complex. Metabolic pathways modulate immune responses and influence immune-cell differentiation and/or activation (Buck et al., 2017; Jung et al., 2019) through competition for resources (such as glucose and oxygen). Drugs that target metabolism can also reduce inflammation (Stathopoulou et al., 2019), for example, rapamycin is an immunosuppressant used for preventing transplant rejection (Thomson et al., 2009) but operates by inhibiting mTOR, a kinase coordinator of metabolic pathways. Similarly, metformin is a T2D drug (targeting adenosine monophosphate—activated protein kinase), but recent studies have suggested that it can help treat skin disorders (Badr et al., 2013).

Previous studies have used MR to identify a causal relationship between BMI and psoriasis (Budu-Aggrey et al., 2019; Ogawa et al., 2019) as well as between BMI and T2D (Corbin et al., 2016; Holmes et al., 2014). Indeed, we found BMI to have a stronger impact on psoriasis and T2D than either disease has on each other. Our genome-wide genetic study reveals four shared loci and a potential causal relationship between psoriasis and T2D independent of BMI. Our MR results suggest that psoriasis may have a causal effect on T2D but are less clear about the effect of T2D on psoriasis. Indeed, psoriasis is believed to have an underlying systemic component (Reich, 2012), and this can increase the risk of T2D (Duncan et al., 2003). Whereas the causal effect of psoriasis on T2D independent of BMI is small (OR = 1.01), the high impact and prevalence of T2D make even a small effect important to consider. Including genome-wide information (as opposed to only established loci) allowed us to increase the power of our analysis; we confirmed that pleiotropy had been taken into account using MR-Egger and addressed the weak instrument bias using MR-RAPS. Nevertheless, selection bias (Haycock et al., 2016) could mean that we underestimated the significance of the causal relationship, and we needed to consider the potential impact of disparity in the number of loci for each trait on the weak instrument bias (BMI has 516 GWS loci, whereas T2D has 176 and psoriasis has 32). Future studies may wish to use a separate selection dataset and/or try different strategies to equalize the number of loci used for each trait to be confident in achieving accurate measurements of effect size.

As an additional means to investigate the genetic correlation between psoriasis and T2D, we applied LD score regression, excluding the major histocompatibility complex owing to the high LD in this region. Using the T2D summary statistics that have not been adjusted for BMI, the genetic correlation with psoriasis was $r_g = 0.157 (P = 1.0 \times 10^{-5})$, whereas using the T2D summary statistics adjusted for BMI, the genetic correlation with psoriasis was $r_g = 0.01$.

Table 2. Frequencies of the Shared Loci in the MGI

<table>
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<tr>
<th>Marker ID</th>
<th>Chr</th>
<th>Position (hg19)</th>
<th>Alleles (Risk and/ or Nonrisk)</th>
<th>RAF Control</th>
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<th>RAF T2D (Only)</th>
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</tbody>
</table>

Abbreviations: Chr, chromosome; ID, identification document; MGI, Michigan Genomics Initiative; RAF, risk allele frequency; T2D, type 2 diabetes.

Genetic Investigation of ANthrometric Traits consortium (Pulit et al., 2019) as a covariate, in addition to the T2D and psoriasis summary statistics, selecting genetic markers (instruments) by LD clumping, which considers both the association and the LD pattern for each locus. We performed MR in a multivariable design (estimating the effect of psoriasis and BMI on T2D as well as T2D and BMI on psoriasis) to simultaneously estimate the causal effect of genetic variants for each trait (Table 3), taking the union of genetic markers (instruments) from the exposures (for completeness, we also provide the single-variable results in Supplementary Table S9). When applying MR using established regions ($P < 5 \times 10^{-8}$), BMI was observed to have a significant causal effect on both T2D ($P = 4.8 \times 10^{-73}$, OR = 2.73) and psoriasis ($P = 1.4 \times 10^{-8}$, OR = 1.73), but we were unable to identify a significant causal relationship between the diseases. By contrast, when using genome-wide information (all loci), we had the power to identify a significant but modest causal relationship for psoriasis on T2D ($P = 1.6 \times 10^{-4}$, OR = 1.01) and a nominally significant causal relationship for T2D on psoriasis ($P = 0.014$, OR = 1.05). The difference in effect sizes between established loci and genome-wide information was negligible (Table 3), suggesting that the results were not biased from using all loci.

To assess the potential impact of any further pleiotropy (besides that due to BMI), we applied two variations of MR beyond the standard (inverse-variance weighted) approach. MR-Egger (Bowden et al., 2015) differs from standard MR because the intercept is included in the model to test and control for pleiotropy because when the effect of the exposures is zero, the outcome should be zero as well. MR-Robust Adjusted Profile Score (RAPS) (Zhao et al., 2019) uses a random effect model to control for pleiotropy and takes into account the variance in the effect sizes used for the exposures. We observed the effect sizes to be consistent when including the intercept in the model and using MR-RAPS. The $P$-values were similar when including or not including the intercept, but their significance was reduced when using MR-RAPS ($P = 0.0128$ for psoriasis on T2D and $P = 0.116$ for T2D on psoriasis). This random effect–based model also supports a modest but significant causal effect of psoriasis on the risk of T2D independent of BMI. There may also be a causal effect of T2D on the risk of psoriasis, but despite the larger effect size, its significance was not as high as for psoriasis on T2D.
the genetic correlation with psoriasis was $r_g = 0.077$ ($P = 0.064$). We believe that this confirms our conclusion from MR that BMI is the dominant factor in the relationship between psoriasis and T2D, and it supports our decision to use the summary statistics adjusted for BMI in our TDMA. It is also interesting that the genetic correlation is close to being nominally significant when adjusting for BMI. Whereas LD score regression and MR are broad-brush approaches, our TDMA approach and colocalization operate at the level of each locus.

For the four shared genetic loci identified, the gene targets are largely involved in immune processes, suggesting that there may be a link between psoriasis and T2D independent of obesity (Supplementary Note S1). Interestingly, whereas the locus in chromosome 11 is negatively associated with BMI, it is positively associated with BMI-adjusted waist-to-hip ratio ($P = 1.6 \times 10^{-11}$, OR = 1.01) (Pulit et al., 2019). Waist-to-hip ratio has been associated with various health conditions, including T2D (Emdin et al., 2017), and it is believed that the distribution of fat can have a significant impact on its role in cardiometabolic disease. We should also consider the potential for patients with type 1 diabetes being misdiagnosed as T2D; however, only the chromosome 17 locus has been previously reported for type 1 diabetes signal within 500 kb (according to the EBI GWAS catalog), and it is not in LD with the locus we identified ($r^2 = 0.003$ in Europeans).

We applied equally weighted TDMA (see Materials and Methods section) rather than the inverse-variance weighted approach typical of meta-analyses for a single trait to avoid biasing results toward T2D, which has a larger sample size than that for the psoriasis cohorts. Compared with other meta-analysis approaches, TDMA revealed the most loci (Supplementary Table S10). Nevertheless, the results are largely consistent, with all techniques revealing the chromosome 10 and chromosome 17 loci and all but association analysis based on subsets revealing the chromosome 11 locus. Association analysis based on subsets also identifies a locus in the major histocompatibility complex (rs9273366), which fits with our hypothesis on the immune basis for shared psoriasis and/or T2D genetics, but the lead marker in our approach was not significant for T2D.

Requiring the $P$-value to be more significant in TDMA than in each disease was designed to avoid false positives. For example, the region around $CDKAL1$ contains GWS signals for both psoriasis and T2D, but previous research has shown that these signals are independent (Quaranta et al., 2009). Our approach does not identify this locus because it is not as significant in TDMA as it is in the individual disease meta-analysis. Weakening the suggestive significance threshold for each disease to $P < 1 \times 10^{-3}$ would allow us to report three more shared loci (Supplementary Table S11), one of which has a gene target (TRAFD1) in the protein–protein

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**Figure 2. Cell type enrichment for TDMA markers outside the MHC.** (a) Calculated using DNAse hotspots in GARFIELD. (b) Using H3K27ac marks from Farh et al. (2015). The enrichment results illustrate immune-cell involvement. diff, differentiation; es, embryonic stem; H3K27ac, histone H3 lysine 27 acetylation; HSMM, human skeletal muscle myoblasts; mem, memory; MHC, major histocompatibility complex; PB, peripheral blood; reg, regulatory; stim, stimulatory; TDMA, trans-disease meta-analysis; Th, T helper.
interaction set for TRAF6. However, patients who have only psoriasis in MGI (Supplementary Table S12) have higher RAF than those with both diseases for the other two loci, suggesting that they may be driven by psoriasis rather than representing a shared mechanism, thus supporting our decision to use the current, more conservative P-value threshold (i.e., \( P < 1 \times 10^{-4} \)).

The MGI RAF for patients with only one of the diseases was lower than that of controls for some loci, and this could be due to interaction with other partially correlated signals from the same region (rather than demonstrating a shared mechanism as we suggested). For example, in chromosome 2, there is another T2D signal \( \sim 400 \) kb away, which does not occur in psoriasis (Supplementary Figure S1). However, LD between this signal and the one identified by TDMA is low (\( r^2 = 0.02 \) in Europeans), and the RAF for this locus is higher in patients with both T2D and psoriasis than in controls.

Although we focused on the differential expression of genes in the TRAF6 protein–protein interaction set, other eQTL targets are differentially expressed. Notably, signal transducer and activator of transcription three gene, \( \text{STAT3} \), is upregulated in psoriatic skin compared with that in controls (fold change = 2.13 in the microarray data and 3.34 in RNA sequencing) as well as in liver (fold change = 2.58) and adipose (fold change = 1.74). \( \text{STAT3} \) binds to NF-κB in competition with IκB (Yang et al., 2007); \( \text{CHUK} \) (IκKα) was downregulated in the pancreas (fold change = 0.44) and liver (fold change = 0.59) of patients with T2D compared with controls and activates NF-κB through the phosphorylation of IκB (Häcker and Karin, 2006). Development of insulin resistance has been linked to IκKβ and/or NF-κB (Shoelson et al., 2007); however, \( \text{CHUK} \) was not differentially expressed in psoriasis. \( \text{CEP68} \) and \( \text{DNMBP} \) are both downregulated in the liver of those with psoriasis and T2D, with \( \text{CEP68} \) being upregulated in the skeletal muscle (fold change = 1.8) and \( \text{DNMBP} \) in the adipose (fold change = 2.17). These genes are involved in centrosome cohesion (Thompson et al., 2004), and centrosome amplification is increased in T2D (Wang et al., 2018).

Interestingly, the lead marker from our chromosome 17 locus is a GWS eQTL (\( P = 3.64 \times 10^{-8} \)) in the glomerulus (Qu et al., 2018) for \( TUBG2 \) (in addition to being a missense variant for this gene) and a suggestive significant eQTL (\( P = 0.048 \)) in the glomerulus (Gillies et al., 2018) for \( \text{BRCA1} \), another gene involved in centrosome regulation. However, we are not able to reveal this as an eQTL signal in normal skin tissue.

By combining summary statistics from large T2D and psoriasis GWAS, we have identified four GWS trans-disease loci (two of which are, to our knowledge, previously unreported findings for one of the diseases). Enrichment analysis suggests that these loci are involved in immune regulation, and this is supported by MR’s detection of a small but significant causal effect of psoriasis on T2D independent of BMI (although the impact of BMI is much larger). We have suggested some potential mechanisms by which the loci may impact psoriasis and T2D, such as the regulation of NF-κB expression through TRAF6. Our work provides a starting point through which efforts can be made at precision medicine to improve the treatment of patients with one or both of these diseases.

Overall, whereas our results suggest that the observed relationship between T2D and psoriasis is largely driven by BMI, the BMI-independent T2D/psoriasis-shared loci revealed by our approach hint at a potential direct causal link between the two conditions.

### MATERIALS AND METHODS

#### Data processing

Data were collected and processed with quality control procedures described in the paper for the GWAS meta-analysis of each trait (Mahajan et al., 2018; Patrick et al., 2018; Vengo et al., 2018). Because T2D and psoriasis have previously been found to be associated with BMI (Takeshita et al., 2017), we used the BMI-adjusted version of the T2D meta-analysis from the DIAbetes Genetics Replication And Meta-analysis consortium (Mahajan et al., 2018) for TDMA. To measure the causal effect of BMI, we used the unadjusted version of the T2D meta-analysis results in MR. All samples are of Caucasian descent, and samples were excluded if they had substantial non-European admixture. Relatedness testing was performed within each meta-analysis to ensure that only independent samples were used but not between studies owing to access limitations for the individual-level data used by the DIAbetes Genetics Replication And Meta-analysis and Genetic Investigation of ANthropometric Traits consortia.

For the identified signals, we calculated the RAF of the lead marker at each locus in 42,112 Caucasian individuals from the MGI

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**Table 3. Multivariable MR**

<table>
<thead>
<tr>
<th>Approach</th>
<th>No of Markers</th>
<th>Psoriasis OR</th>
<th>Psoriasis P</th>
<th>BMI OR</th>
<th>BMI P</th>
<th>T2D OR</th>
<th>T2D P</th>
<th>BMI OR</th>
<th>BMI P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established (( P &lt; 5 \times 10^{-8} )) loci</td>
<td>IVW (standard)</td>
<td>548</td>
<td>1.01</td>
<td>0.528</td>
<td>2.73</td>
<td>4.84 \times 10^{-71}</td>
<td>650</td>
<td>1.06</td>
<td>0.095</td>
</tr>
<tr>
<td>MR-Egger</td>
<td>1.01</td>
<td>0.506</td>
<td>2.73</td>
<td>7.70 \times 10^{-71}</td>
<td>1.06</td>
<td>0.096</td>
<td>1.37</td>
<td>1.59 \times 10^{-4}</td>
<td></td>
</tr>
<tr>
<td>MR-RAPS</td>
<td>1.02</td>
<td>0.363</td>
<td>2.60</td>
<td>2.07 \times 10^{-70}</td>
<td>1.04</td>
<td>0.215</td>
<td>1.35</td>
<td>4.49 \times 10^{-4}</td>
<td></td>
</tr>
<tr>
<td>Genome-wide information</td>
<td>IVW (standard)</td>
<td>3,749</td>
<td>1.01</td>
<td>1.59 \times 10^{-4}</td>
<td>2.59</td>
<td>3.07 \times 10^{-304}</td>
<td>3,703</td>
<td>1.05</td>
<td>0.014</td>
</tr>
<tr>
<td>MR-Egger</td>
<td>1.01</td>
<td>1.36 \times 10^{-4}</td>
<td>2.59</td>
<td>1.90 \times 10^{-303}</td>
<td>1.05</td>
<td>0.016</td>
<td>1.35</td>
<td>1.64 \times 10^{-7}</td>
<td></td>
</tr>
<tr>
<td>MR-RAPS</td>
<td>1.00</td>
<td>0.0128</td>
<td>2.26</td>
<td>1.37 \times 10^{-174}</td>
<td>1.04</td>
<td>0.116</td>
<td>1.29</td>
<td>2.70 \times 10^{-5}</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; IVW, inverse-variance weighted; MR, Mendelian randomization; No, number; RAPS, Robust Adjusted Profile Score; T2D, type 2 diabetes.
exposures were fitted in a multivariable regression to model the genetic markers across the traits. For the MR-Base approach, all the in the summary statistics for each trait on the intersection of ge-
LD through LD clumping using the 1,000 Genomes European samples analysis (i.e., including BMI as a covariate) on markers identified MR was performed using both univariable and multivariable effective and robust when used with genome-wide information).

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(fritsche et al., 2018), which contains genotypes linked to electronic health records, allowing us to evaluate the loci in a hospital-based study. By using the International Classification of Diseases 9 and/ or 10 codes to define disease status (Supplementary Note S2), we identified 8,622 patients with T2D only, 783 patients with psoriasis only, 344 patients with both psoriasis and T2D, and 32,363 controls with neither disease. To the best of our knowledge, written informed consent was obtained in the MGI project (Fritsche et al., 2018) and in each of the cohorts included in the summary statistics (Mahajan et al., 2018; Patrick et al., 2018; Yengo et al., 2018).

**TDMA**

We avoided biasing results toward the disease with the largest sample size (T2D) by conducting TDMA using an equally weighted combination of effect sizes and variances from the meta-analysis for each disease (Supplementary Note S3). We then filtered these results to only select loci for which the TDMA lead marker was (i) GWS ($P < 5 \times 10^{-8}$) in TDMA, (ii) suggestively significant ($P < 1 \times 10^{-5}$) in the individual meta-analyses, and (iii) more significant in TDMA than in both the individual meta-analyses. We also compared our approach with existing meta-analysis methods. Colocalization was performed between the psoriasis and T2D summary statistics for each locus using Coloc (Giambartolomei et al., 2014). The identified loci were interpreted through chromatin marks, eQTLs, differential expression, promoter capture Hi-C, and protein–protein interaction enrichment (Supplementary Note S4).

**MR**

We applied MR to test for a causal relationship between psoriasis and T2D. MR was performed using MR-Base (Hemani et al., 2018) (an R package that envelops a wide range of MR techniques) and MR-RAPS (Zhao et al., 2019) (a recent technique shown to be effective and robust when used with genome-wide information). MR was performed using both univariable and multivariable analysis (i.e., including BMI as a covariate) on markers identified through LD clumping using the 1,000 Genomes European samples (LD $\leq 0.001$, window size = 10 megabase pair) and the P-values in the summary statistics for each trait on the intersection of genetic markers across the traits. For the MR-Base approach, all the exposures were fitted in a multivariable regression to model the outcome (e.g., $\beta_{\text{BMI}} \sim \beta_{\text{T2D}} + \beta_{\text{RAU}}$).

**Data availability statement**

Data from the DiAbetes Genetics Replication And Meta-analysis (https://www.diabetes-consortium.org) and Genetic Investigation of ANthropometric Traits (https://portals.broadinstitute.org/collaboration/giant) consortia may be found on their respective websites. The psoriasis summary statistics are available on request.

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**CONFLICT OF INTEREST**

JEG received research grants from AbbVie, AnaptyxBio, Pfizer, Novartis, Celgene, and Eli Lilly and serves on advisory board in Novartis, AbbVie, Eli Lilly, Meragen, and Almirall. NNM is a full-time United States government employee and has served as a consultant for Amgen, Eli Lilly, and Leo Pharma receiving grants and/or other payments: as a principal investigator and/or investigator for AbbVie, Celgene, Janssen Pharmaceuticals, and Novartis receiving grants and/or research funding; and as a principal investigator for the National Institute of Health receiving grants and/or research funding.

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**SUPPLEMENTAL MATERIAL**

Supplemental material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2020.11.025.

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