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Causal relationship and shared genetic loci between psoriasis and type 2 diabetes through trans-disease meta-analysis

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Abstract

Psoriasis and type 2 diabetes (T2D) are complex conditions with significant impact on health. Psoriasis patients have higher risk of type 2 diabetes (~1.5 Odds Ratio) and vice versa, controlling

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Conflict of interest

JEG received research grants from AbbVie, AnaptysBio, Pfizer, Novartis, Celgene, and Eli Lilly, and serves as advisory board in Novartis, AbbVie, Eli Lilly, MiRagen, and Almirall. NNM is a full-time US government employee and has served as a consultant for Amgen, Eli Lilly, and Leo Pharma receiving grants/other payments; as a principal investigator and/or investigator for AbbVie, Celgene, Janssen Pharmaceuticals, Inc, 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.

for body mass index (BMI), yet there has been limited study comparing their genetic architecture. We hypothesized there are shared genetic components between psoriasis and T2D. Trans-disease meta-analysis (TDMA) was applied to 8,016,731 well-imputed genetic markers from large-scale meta-analyses of psoriasis (11,024 cases and 16,336 controls) and T2D adjusted for BMI (74,124 cases and 824,006 controls). We confirmed our findings in a hospital-based study (42,112 patients) and tested for causal relationships with multi-variable Mendelian randomization. Mendelian randomization identified a causal relationship between psoriasis and T2D ($p=1.6x10^{-4}$, OR=1.01), and highlighted the impact of BMI. TDMA further revealed 4 genome-wide significant loci ($p<5x10^{-8}$) with evidence of colocalization, and shared directions of effect between psoriasis and T2D not present in BMI. Proteins coded by genes in these loci (ACTR2, ERLIN1, TRMT112, and BECN1) are connected through NF-κB signaling. Our results provide insight into the immunological components which connect immune-mediated skin conditions and metabolic diseases, independent of confounding factors.

Keywords

Psoriasis; Genome-Wide Association Studies (GWAS); Epidemiology; Inflammation; Bioinformatics

Introduction

Psoriasis is a complex skin disease, which affects over 7 million adults in the USA (Rachakonda et al.,2014), causing painful lesions and itching. Furthermore, psoriasis comorbidities account for more than half the direct healthcare costs (Brezinski et al., 2015, Feldman et al., 2017, Pilon et al., 2019, Vanderpuye-Orgle et al., 2015). Diabetes, the seventh leading cause of death in the USA (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 type 2 diabetes (T2D) and psoriasis are significantly associated, with reported Odds Ratios (ORs) of approximately 1.5 (Dubreuil et al., 2014, Hemminki et al., 2015), after controlling for Body Mass Index (BMI) and other covariates. Psoriasis patients exhibit reduced incretin effect (Gyldenlove et al., 2015), insulin secretion in response to oral glucose, which is considered to be indicative of prediabetes. Notably, patients with higher severity of psoriasis (i.e. more extensive skin involvement) were found to be at 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. While large-scale genome-wide association studies 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 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 Th1 signaling, as well as 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 genome-wide association studies (GWAS) of previously established consortia for the two diseases, our aim is 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 to unravel causal relationships and identified 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 824,006 controls from the DIAGRAM consortium (Mahajan et al., 2018)), using 8,016,731 well-imputed markers common to both cohorts. We then performed multi-variable Mendelian randomization, with BMI summary statistics from 806,834 samples in the GIANT consortium as a covariate (Pulit et al., 2019).

Shared Loci Identified

43 "shared loci" (Supplementary Table 1) and 32 "opposing loci" (Supplementary Table 2) were genome-wide significant ($p<5x10^{-8}$) in TDMA, when combining effect in the same or opposing direction across the two diseases, respectively. Among these associations, 11 shared and 4 opposing loci had stronger evidence of association (more significant p-value) in TDMA than the individual meta-analysis for each disease.

We investigated the loci with suggestive evidence of association ($p<1x10^{-4}$) in each of the two diseases. Four shared disease loci (Table 1; Supplementary Figure 1) met this criterion: 2p14 ($p=9.6x10^{-9}$); 10q24.31 ($p=1.0x10^{-9}$); 11q13.1 ($p=1.0x10^{-}$); and 17q21.2 ($p=1.5x10^{-9}$). We further note these loci have significantly higher colocalization (between psoriasis and T2D) posterior probability (Mann-Whitney p=5.7x10^{-4}) than the 59 other previously reported loci for psoriasis (Supplemental Figure 2), for example the signal in chromosome 10 has 0.97 posterior probability of being a shared locus. The chromosome 10 locus (Figure 1b) is suggestive significant in each disease meta-analysis ($p=1.6x10^{-6}$ for psoriasis and $p=7.1x10^{-7}$ for T2D) but genome-wide significant ($p=1.0x10^{-9}$) in TDMA.

This locus is of particular interest as the lead trans-disease marker (rs12265333) is 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 body mass index (BMI) in summary statistics from the GIANT consortium (Pulit et al., 2019) and the effect of the BMI signal is in the opposite direction to that of the psoriasis and T2D signal, suggesting they are not on the same haplotype.

In the MGI data, the risk allele frequencies (RAF) for the lead marker at each of the four loci were higher (8% on average) for patients with both diseases than controls (Table 2). Interestingly, for all but the 2p14 loci, the RAF is higher for controls than patients with only one of the diseases, suggesting our TDMA approach performs 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 genome-wide significant signal for psoriasis ($p=6.6x10^{-5}$ in psoriasis meta-analysis), as is the chromosome 11 locus (11q13.1) for T2D ($p=7.8x10^{-5}$ in T2D meta-analysis).

Functional Interpretation of Shared Loci

To investigate which cell types are affected by the shared psoriasis/T2D genetic signals, we applied GARFIELD (Iotchkova et al., 2019) to evaluate the overlap between different chromatin marks with the LD-independent significant markers in the TDMA (analysis restricted to markers more significant in TDMA than 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 3), with 48 out of 60 (80%) DNase-seq experiments having their hypersensitive sites significantly overlapping with disease-shared loci after Bonferroni correction (i.e. $p<9.7x10^{-5}$), indicating potential immune-cell involvement.

We repeated the enrichment analysis after excluding the MHC region and found 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 3). 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 cell in general. We then applied GARFIELD to active regulatory elements measured by H3K27ac marks in different immune cells (Farh et al., 2015). Interestingly, Th17 cells were now the most significant ($p=4.8x10^{-8}$), overlapping in particular our chromosome 10 and 17 loci, and other immune-cell types were also more enriched (Figure 2b) than lymphoblastoids in GARFIELD's default annotation set. These results illustrate specific immune-cell involvement shared between the diseases, with Th17 cells having a key role in the development of psoriasis (Di Cesare et al.,2009) and suggested involvement in type 2 diabetes (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 linkage disequilibrium (r^2=0.94) with a missense variant for *CHUK*. However, SIFT (Kumar et al., 2009) and PolyPhen-2 (Adzhubei et al., 2013) suggest these mutations are unlikely to have strong deleterious effect on protein function.

Therefore, instead of focusing on the best signal in the trans-disease meta-analysis, 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 trans-disease meta-analysis (TDMA) than either of the individual traits at 3 of the 4 loci (Supplementary Table 4). We then recorded the CADD (Combined Annotation Dependent Depletion) score for each marker in the intersection of the credible sets (Rentzsch et al., 2019) (TDMA/psoriasis/T2D) for each locus (Supplementary Table 5), and identified all their significant cis-eQTL gene targets (FDR<0.05) in three different eQTL datasets for blood (Jansen et al., 2017, Vosa et al., 2018, Westra et al., 2013). The PHRED-scaled CADD score for 6 of the markers (in chromosome 2 and 10) was higher than 10.0, indicating 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 it is in the top 1%. According to the three blood eQTL databases, the expression of 34 genes in 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 6). Significantly, the PHRED-scaled CADD score for the most significant eQTL of each gene (mean: 7.1; SD: 2.6) is significantly higher (Wilcoxon rank sum test $p=2.76x10^{-3}$) 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 CADD score for eQTLs in the intersection of the credible sets than the full set of eQTLs for each gene from the database (Supplementary Table 7), suggesting the markers identified by our approach are more likely to have 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 (PPI) dataset (Chen et al., 2012) to interact with the hub protein TRAF6 (enrichment $p=1.3x10^{-6}$). TRAF6 mediates NF-κB expression and has previously been implicated in the development of both psoriasis (Huffmeier et al., 2010) and type 2 diabetes (Balasubramanyam et al., 2011). *ACTR2* ($p=5.0x10^{-18}$, fold change=1.85) and *TRMT112* ($p=5.4x10^{-13}$, fold change=1.57) were found to be up-regulated in microarray (Gudjonsson et al., 2009) and RNA-seq (Tsoi et al., 2019) differential expression analysis, respectively (Supplementary Table 8) for lesional psoriatic compared to healthy skin. *ACTR2* was also up-regulated in skeletal muscle (Wu et al., 2007) ($p=8.7x10^{-12}$, fold change=1.76) and the subcutaneous adipose tissue (Soronen et al., 2012) ($p=2.4x10^{-2}$, fold change=1.58) from type 2 diabetes patients compared to healthy controls, but down-regulated in the pancreas (Dominguez et al., 2011)($p=1.6x10^{-2}$, fold change=0.31). Similarly, *BECN1* was up-regulated in skeletal muscle ($p=5.4x10^{-7}$, fold change=1.70) and down-regulated in pancreas ($p=3.3x10^{-2}$, fold change=0.48), and both *TRMT112* ($p=4.8x10^{-3}$, fold change=0.63) and *ERLIN1* ($p=2.7x10^{-3}$, fold change=0.57) were down-regulated in the pancreas of T2D patients compared to healthy controls.

Mendelian randomization (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), Mendelian randomization 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 GIANT consortium (Pulit et al., 2019) as a covariate, in addition to the T2D and psoriasis summary statistics, selecting genetic markers (instruments) by linkage disequilibrium (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 9). When applying MR using established regions ($p<5x10^{-}$), BMI is observed to have a significant causal effect on both T2D ($p=4.8x10^{-73}$, OR=2.73) and psoriasis ($p=1.4x10^{-4}$, 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 have power to identify a significant but modest causal relationship for psoriasis on T2D ($p=1.6x10^{-4}$, 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 is negligible (Table 3), suggesting the results are 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 in that the intercept is included in the model to test and control for pleiotropy, since when the effect of the exposures is zero, the outcome should be zero as well. MR-RAPS (Zhao et al., 2018) 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.

Discussion

The relationship between immune-mediated skin diseases and metabolic disorders is highly complex. Metabolic pathways modulate immune responses and influence immune cell differentiation/activation (Buck et al., 2017, Jung et al., 2019) through competition for resources (such as glucose and oxygen). Drugs which 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 AMP-activated protein kinase) but recent studies have suggested it can help treat skin disorders (Badr et al., 2013).

Previous studies have used Mendelian randomization 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 work represents, to our knowledge, the first genome-wide based genetic study and reveals four shared loci and a potential causal relationship between psoriasis and T2D independent of BMI. Our Mendelian randomization results suggest 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). While the causal effect of psoriasis on T2D independent of BMI is small (OR=1.01), the high impact and prevalence of T2D makes 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 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 we underestimate the significance of the causal relationship and we need to consider the potential impact of disparity in number of loci for each trait on the weak instrument bias (BMI has 516 genome-wide significant loci, while 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 MHC due 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=1.0x10^{-5}), while using the T2D summary statistics adjusted for BMI, the genetic correlation with psoriasis was r_g=0.077 (p=0.064). We believe this confirms our conclusion from Mendelian Randomization 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 trans-disease meta-analysis. It is also interesting that the genetic correlation is close to being nominally significant when adjusting for BMI. While LD score regression and Mendelian randomization are ‘broad brush’ approaches, our trans-disease meta-analysis approach and colocalization operate at the level of each locus.

For the 4 shared genetic loci identified, the gene targets are largely involved in immune processes, suggesting there may be a link between psoriasis and T2D independent of obesity (Supplementary Note 1). Interestingly, while the locus in chromosome 11 is negatively associated with BMI, it is positively associated with BMI-adjusted waist-to-hip ratio ($p=1.6x10^{-14}$, OR=1.01) (Pulit et al., 2019). Waist-to-hip ratio has been associated with various health conditions including type 2 diabetes (Emdin et al., 2017), and it is believed 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 (T1D) being misdiagnosed as T2D, however only the chromosome 17 locus has a previously reported for

T1D signal within 500kb (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 Methods), rather than the inverse-variance weighted (IVW) approach typical of meta-analyses for a single trait, to avoid biasing results towards T2D, which has a larger sample size compared with the psoriasis cohorts. Compared to other meta-analysis approaches, TDMA revealed the most loci (Supplementary Table 10). Nevertheless, the results are largely consistent, with all techniques revealing the chromosome 10 and chromosome 17 loci, and all but ASSET revealing the chromosome 11 locus. ASSET also identifies a locus in the MHC (rs9273366), which fits with our hypothesis on the immune basis for shared psoriasis/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 each disease was designed to avoid false positives. For example, the region around *CDKAL1* contains genome-wide significant signals for both psoriasis and T2D but previous research has shown these signals are independent (Quaranta et al., 2009). Our approach does not identify this locus, as 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 $p<1x10^{-3}$ would allow us to report three more shared loci (Supplementary Table 11), one of which has a gene target (*TRAFD1*) in the PPI set for TRAF6. However, psoriasis-only patients in MGI (Supplementary Table 12) have higher risk allele frequency than those with both diseases for the other two loci, suggesting 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. $p<1x10^{-4}$).

The MGI risk allele frequency 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 ~400kb away which does not occur in psoriasis (Supplementary Figure 1). 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 both T2D and psoriasis patients than controls.

Although we focused on the differential expression of genes in the TRAF6 PPI set, other eQTL targets are differentially expressed. Notably, *STAT3* is upregulated in psoriatic skin compared to controls (fold change=2.13 in the microarray data and 3.34 in RNA-seq), as well as in liver (fold change=2.58) and adipose (fold change=1.74). *STAT3* binds to NF-κB in competition with I-κB (Yang et al., 2007); *CHUK* (IKKa) was downregulated in T2D pancreas (fold change=0.44) and liver (fold change=0.59) compared to controls and activates NF-κB through phosphorylation of I-κB (Hacker and Karin, 2006). Development of insulin resistance has been linked to IKKP/NF-κB (Shoelson et al., 2007), however, *CHUK* was not differentially expressed in psoriasis. *CEP68* and *DNMBP* are both downregulated in psoriasis and T2D liver, with *CEP68* being upregulated skeletal muscle (fold change=1.8) and *DNMBP* in 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 genome-wide significant eQTL ($p=3.64x10^{-8}$) in glomerulus (Qiu et al., 2018) for *TUBG2* (in addition to being a missense variant for this gene) and a suggestive significant eQTL ($p=0.048$) in glomerulus (Gillies et al., 2018) for *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 genome-wide significant trans-disease loci (two of which are, to our knowledge, previously unreported findings for one of the diseases). Enrichment analysis suggests these loci are involved in immune regulation, and this is supported by Mendelian randomization'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, while our results suggest 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, Yengo et al., 2018). Since 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 DIAGRAM 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 Mendelian randomization. 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 only independent samples were used, but not between studies, due to access limitations for the individual-level data used by the DIAGRAM and GIANT consortia.

For the identified signals, we calculated the risk allele frequencies (RAF) of the lead marker at each locus in 42,112 Caucasian individuals from the Michigan Genomics Initiative (MGI) (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 ICD9/10 codes to define disease status (**Supplementary Note 2**), 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).

Trans-disease meta-analysis (TDMA)

We avoided biasing results towards the disease with 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 3). To our knowledge, our study represents the first time this approach has been applied. We then filtered these results to only select loci for which the TDMA **lead marker** is: 1) genome-wide significant ($p<5x10^{-8}$) in TDMA; 2) suggestive significant ($p<1x10^{-4}$) in the individual meta-analyses; and 3) more significant in TDMA than 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 PPI enrichment (Supplementary Note 4).

Mendelian randomization

We applied Mendelian randomization to test for causal relationship between psoriasis and T2D. MR was performed using MR-Base (Hemani et al., 2016) (an R package which envelops a wide range of MR techniques) and MR-RAPS (Zhao et al., 2018) (a recent technique shown to be effective and robust when used with genome-wide information). Mendelian randomization was performed using both uni- and multi-variable analysis (i.e. including BMI as a covariate), on markers identified through linkage disequilibrium (LD) clumping using the 1000 Genomes European samples (LD≥0.001, window size=10Mbp) 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 multi-variable regression to model the outcome (e.g. $\beta_{PsV} \sim \beta_{T2D} + \beta_{BMI}$).

Data Availability

Data from the DIAGRAM (https://www.diagram-consortium.org) and GIANT (https://portals.broadinstitute.org/collaboration/giant) consortium may be found on their respective websites. The psoriasis summary statistics are available upon request.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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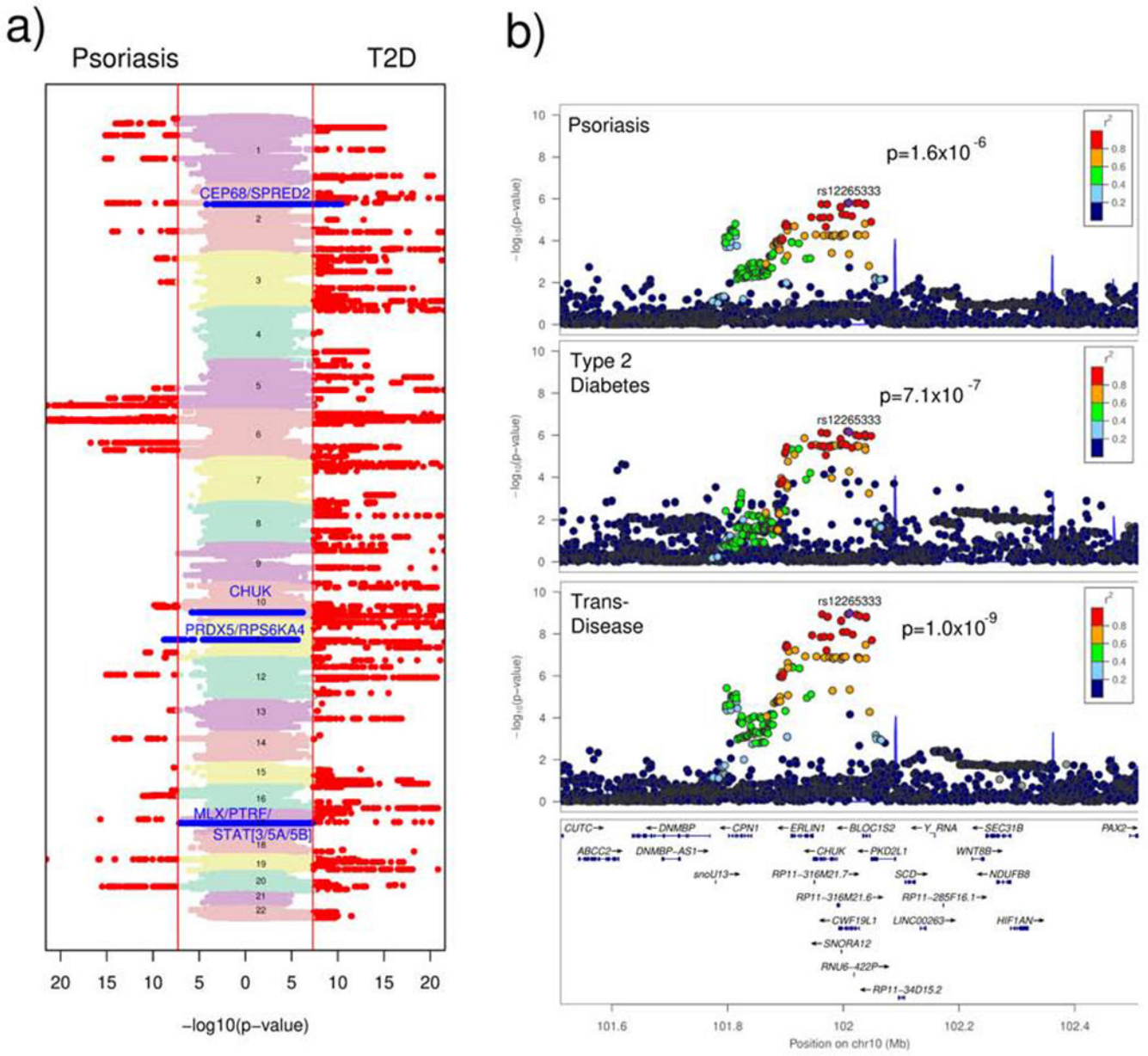

Figure 1: Trans-disease Meta-analysis.

a) Vertical Manhattan plots of the meta-analysis association results for psoriasis and T2D, showing genome-wide significant ($p \leq 5x10^{-8}$) markers in **red** and shared loci identified by our trans-disease meta-analysis in **blue**. b) Regional association plots for the chromosome 10 locus in psoriasis and T2D (with the lead marker in purple). The locus is suggestive significant for each disease and genome-wide significant in the trans-disease meta-analysis.

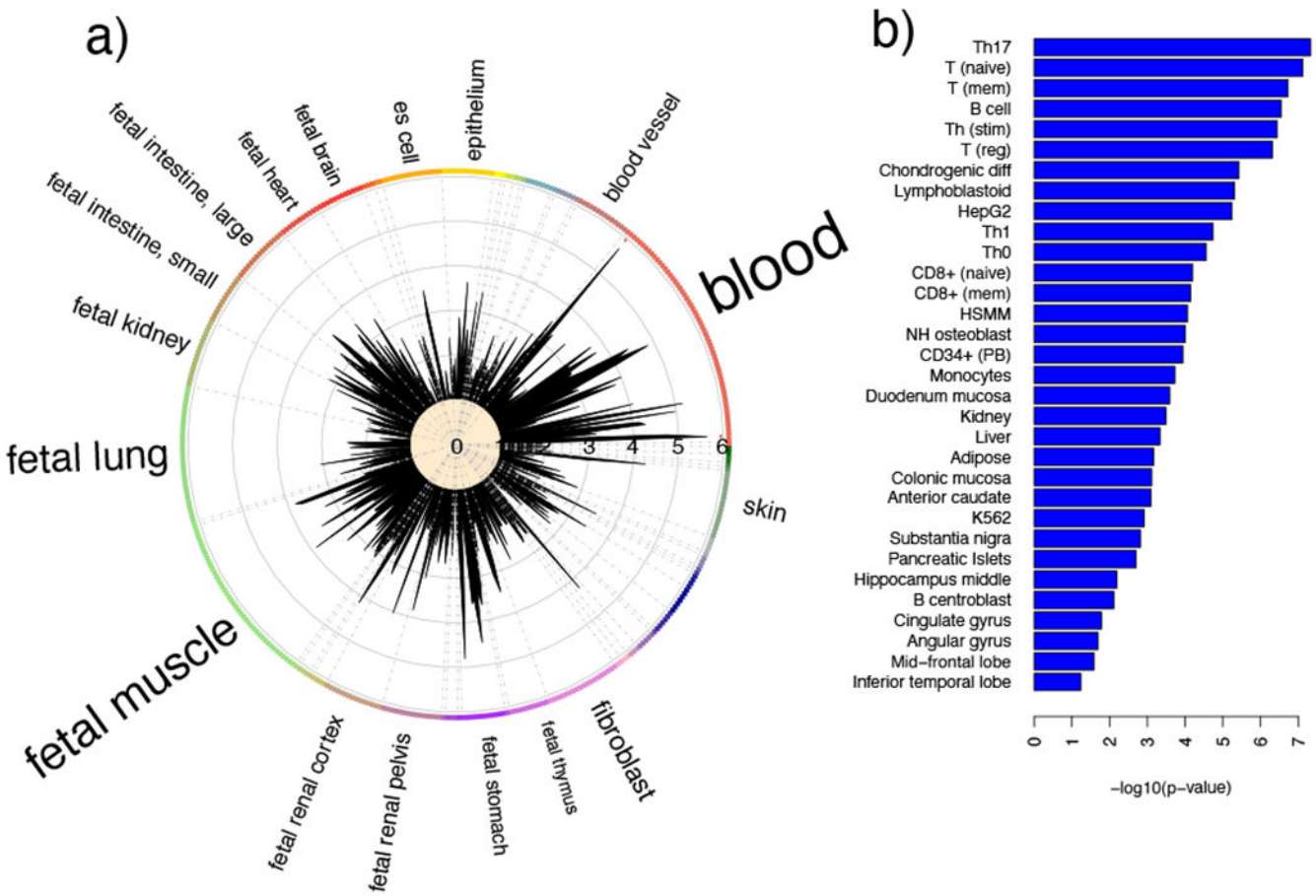

Figure 2: Cell Type Enrichment for Trans-Disease Meta-Analysis Markers Outside the MHC.

a) Calculated using DNAse hotspots in GARFIELD. b) Using H3K27ac marks from Farh et al.(Farh et al., 2015) The enrichment results illustrate immune-cell involvement.

Table 1:

Trans-disease meta-analysis results for loci meeting criteria

Marker ID	Chr	Position (hg19)	Alleles (risk/ non-risk)	Meta-analysis P-values			Meta-analysis Odds Ratios			Minor Allele Frequencies[a]		Nearby Gene	BMI Locus?[b]	New[c] GWAS Locus?[b]
				P(Psoriasis)	P(T2D)	P(Both)	OR(Psoriasis)	OR(T2D)	OR(Both)	Psoriasis	T2D			
rs840967	2	65701757	C/A	$6.6x10^{-5}$	$4.4x10^{-8}$	$9.6x10^{-9}$	1.08	1.04	1.06	0.40	0.41	*SPRED2*	No	Psoriasis
rs12265333	10	102011211	A/G	$1.6x10^{-6}$	$7.1x10^{-7}$	$1.0x10^{-9}$	1.12	1.04	1.08	0.49	0.49	*CHUK*	No	No
rs685870	11	64111928	T/C	$8.5x10^{-9}$	$7.8x10^{-5}$	$1.0x10^{-11}$	1.13	1.03	1.08	0.31	0.30	*PRDX5*	Yes[d]	T2D
rs2292749	17	40818584	T/C	$4.3x10^{-6}$	$1.5x10^{-6}$	$1.5x10^{-9}$	1.10	1.04	1.07	0.29	0.30	*STAT3*	No	No

Abbreviations are as follows: Chr, chromosome; OR, odds ratio; p, p-value; T2D, type 2 diabetes; BMI, body mass index; GWS, genome-wide significant (i.e. $p<5x10^{-8}$).

[a] Minor alleles are provided for each entire meta-analysis (cases and controls), rather than specigically for each disease.

[b] We determine whether a locus is previously known to be associated with BMI, psoriasis, or T2D according to data from the GIANT and DIAGRAM consortium, as well as a search of the available literature.

[c] To our knowledge, previously unreported.

[d] The lead marker of the chromosome 11 locus (rs685870) is significantly associated with BMI in the GIANT consortium meta-analysis ($2.3x10^{-9}$), but its effect (OR=1.01) is in the opposite direction to the signal we identified in our trans-disease meta-analysis (i.e. the risk allele is C rather than T), suggesting it is not in the same haplotype.

Table 2:

Frequencies of the Shared Loci in the Michigan Genomics Initiative

Marker ID	Chr	Position (hg19)	Alleles (risk/non-risk)	Risk Allele Frequency			
				Control	Psoriasis (only)	T2D (only)	Both
rs840967	2	65701757	C/A	0.398	0.416	0.404	0.434
rs12265333	10	102011211	A/G	0.510	0.511	0.502	0.515
rs685870	11	64111928	T/C	0.306	0.301	0.307	0.331
rs2292749	17	40818584	T/C	0.284	0.282	0.293	0.325

Abbreviations are as follows: Chr, chromosome; T2D, type 2 diabetes.

Table 3:

Multi-Variable Mendelian Randomization

	Approach	Psoriasis + BMI on T2D					T2D + BMI on Psoriasis				
		Num. Markers	Psoriasis		BMI		Num. Markers	T2D		BMI	
			OR	*P*	*OR*	*P*		*OR*	*P*	*OR*	*P*
Established ($p<5x10^{-8}$) loci	IVW (standard)	548	1.01	0.528	2.73	$4.84x10^{-73}$	650	1.06	0.095	1.37	$1.44x10^{-4}$
	MR-Egger		1.01	0.506	2.73	$7.70x10^{-73}$		1.06	0.096	1.37	$1.59x10^{-4}$
	MR-RAPS		1.02	0.363	2.60	$2.07x10^{-70}$		1.04	0.215	1.35	$4.49x10^{-4}$
Genome-wide information	IVW (standard)	3,749	1.01	$1.59x10^{-4}$	2.59	$3.07x10^{-304}$	3,703	1.05	0.014	1.35	$1.40x10^{-7}$
	MR-Egger		1.01	$1.36x10^{-4}$	2.59	$1.90x10^{-303}$		1.05	0.016	1.35	$1.64x10^{-7}$
	MR-RAPS		1.01	0.0128	2.26	$1.37x10^{-174}$		1.04	0.116	1.29	$2.70x10^{-5}$

Abbreviations are as follows: IVW, inverse variance weighted; Num., number of; T2D, type 2 diabetes; BMI, body mass index; OR, odds ratio; p, p-value.