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Identifying Novel Psoriatic Disease Drug Targets Using a Genetics-Based Priority Index Pipeline

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Abstract

Background: Despite numerous genome-wide association studies conducted in psoriasis and psoriatic arthritis, only a small fraction of the identified genes has been therapeutically targeted.

Objective: We sought to identify and analyze potential therapeutic targets for psoriasis and psoriatic arthritis (PsA) using the priority index (Pi), a genetics-dependent drug target prioritization approach.

Methods: Significant genetic variants from GWAS for psoriasis, PsA, and combined psoriatic disease were annotated and run through the Pi pipeline. Potential drug targets were identified based on genomic predictors, annotation predictors, pathway enrichment, and pathway crosstalk.

Results: Several gene targets were identified for psoriasis and PsA that demonstrated biological associations to their respective diseases. Some are currently being explored as potential therapeutic targets (i.e. ICAM1, NF-kB, REV3L, ADRA1B for psoriasis; CCL11 for PsA); others have not yet been investigated (i.e. LNPEP, LCE3 for psoriasis; UBLCP1 for PsA). Additionally, many nodal points of potential intervention were identified as promising therapeutic targets. Of these, some are currently being studied such as TYK2 for psoriasis, and others have yet to be explored (i.e. PPP2CA, YAP1, PI3K, AKT, FOXO1, RELA, CSF2, IFNGR1, IFNGR2 for psoriasis; GNAQ, PLCB1, GNAI2 for PsA).

Conclusion: Through Pi, we identified data-driven candidate therapeutic gene targets and pathways for psoriasis and PsA. Given the sparse PsA specific genetic studies and PsA specific drug targets, this analysis could prove to be particularly valuable in the pipeline for novel psoriatic therapies.

Conflicts of Interest: Dr. Liao has received research grant support from Abbvie, Amgen, Janssen, Leo Pharma, Novartis, Pfizer, Regeneron, and TRex Bio.

Keywords

psoriasis; psoriatic arthritis; drug targets; priority index; genetics-based discovery

Introduction

Psoriasis is a chronic immune-mediated inflammatory disease characterized by thick, erythematous and scaly plaques that affects 3.2% of adults in the United States and up to 3.0% of the world population.[1,2] Comorbidities classically associated with psoriasis include cardiovascular disease, metabolic syndrome, and inflammatory bowel disease. This occurrence may be due to shared risk factors or systemic inflammatory mediators.[3] While environmental triggers such as stress, mechanical trauma, and infection are known contributors to the development of psoriasis, population and family-based studies suggest that there is a genetic component in the disease development as well.[4–6]

Psoriatic arthritis (PsA) affects up to one-third of patients with psoriasis but has a prevalence of about 0.3–1% in the general population.[7–9] Psoriasis generally precedes PsA, on average by 10 years.[7,10] PsA involves inflammation of the joints, spine, and surrounding structures, resulting in pain, swelling, stiffness, and limited motion. While the exact pathogenesis of psoriasis and PsA is yet to be fully elucidated, many targeted therapies exist for the treatment of both psoriasis and PsA.

Current biologics available for the treatment of psoriasis include tumor necrosis factor (TNF)-α inhibitors, interleukin (IL)-12 /IL-23 inhibitors, IL-17 inhibitors, and IL-23 inhibitors.[11] Many of these treatments are also used for managing PsA symptoms and progression.[12] Current small molecules used for psoriatic disease treatment include phosphodiesterase (PDE) inhibitors such as apremilast and janus kinase (JAK) inhibitors such as tofacitinib, while older agents include methotrexate, acitretin, and cyclosporine. A_3 adenosine receptor agonists such as CF101 are being explored for the treatment of psoriasis.[11] In general, these small molecules work to downregulate pro-inflammatory cytokines that significantly contribute to psoriasis. Despite these treatment options, exploring novel therapeutic mechanisms has the potential to advance the field.

Over the past decade, there has been groundbreaking work in identifying genetic variants associated with specific diseases. The findings from these genome-wide association studies (GWAS) traditionally have yielded only a select number of therapeutic targets. However, more sophisticated and powerful approaches are being developed to mine GWAS data for new drug targets. Analyses have shown that potential drugs within the drug development pipeline are twice as likely to be approved if it has human genetic evidence of disease association, supporting the increased use of genetics in drug development.[13,14]

Although drug targets with genetic evidence have a higher likelihood of being therapeutically advantageous, translating GWAS data for drug target discovery remains a challenge especially for complex diseases. A recently published algorithm that addresses this challenge is the priority index (Pi) pipeline.[15] Pi uses GWAS single nucleotide polymorphisms (SNPs) as inputs and uses genomic and immune-related annotations to

assign a score from 0 to 5 indicating how likely a gene is to be responsible for the GWAS signal ("seed genes"). These scores are based on 1) genomic proximity to disease-associated SNPs (nGene score) which accounts for the linear genomic organization and linkage disequilibrium; 2) chromatin conformation capture genes (cGene) which accounts for interactions between loci that are close in 3D space even if they are separated along the linear genome; and 3) modulation of gene expression based on expression quantitative trait loci (eQTL; eGene) which accounts for the high enrichment of eGenes for drug targets.[15] Additional annotation predictors are used to modulate the score of seed genes: immune function (fGene), immune phenotype (pGene), and rare genetic immune diseases (dGene).[15] Interestingly, the Pi developers' work showed that the interacting neighbors of GWAS-reported genes ("non-seed genes") were usually known drug targets rather than the actual GWAS-reported genes themselves.[15] This is supported by other studies that use pathway and gene interaction networks to more accurately identify drug targets.[16,17] For this reason, the Pi pipeline also takes into account network connectivity in order to enhance scoring for both non-seed genes and seed genes with evidence of connectivity. The Pi pipeline can determine pathways most significantly enriched for highly prioritized targets as well as identify potential nodes of intervention by both determining crosstalk between these pathways and by maximizing the number of highly prioritized interconnecting genes.[15]

Using GWAS data, we identified highly scored genes, enriched pathways, and potential nodal points of intervention (defined here as any node within the prioritized gene network with greater than six edges) for psoriasis, PsA, and combined psoriatic diseases. In our analyses, we were able to confirm current drug targets for psoriasis and PsA as well as reveal GWAS-derived novel targets that have yet to be fully explored. Interestingly, we were able to identify potential drug targets unique to PsA that were not identified in either the psoriasis analysis or the combined psoriatic disease analysis. Overall, these findings expand our knowledge of potential treatment targets for both psoriasis and psoriatic arthritis.

Methods

Data collection and processing

Psoriasis and PsA SNP variants and p-values were obtained in December 2020 from the publicly available GWAS catalog.[18] The GWAS catalog contained 16 psoriasis studies (containing 185 SNPs) and 5 psoriatic arthritis studies (containing 59 SNPs). We curated a list of psoriasis SNPs that did not include PsA variants, a separate list of PsA SNPs, and a combined psoriatic disease list that included all psoriasis and PsA variants (Supplementary Table 1). Variants were excluded if they were from multi-disease studies in which psoriasis was combined with another non-psoriatic disease. If more than one study identified the same variant, only the lowest p-value was retained.

Gene and pathway prioritization

All analyses were performed using the Priority Index *Pi* 1.13.1 package in R 3.6.3. Analyses were performed with default parameters and monocyte eQTLs as the most relevant available dataset.[19]

Literature searches using the PubMed Database were conducted on all genes identified by the priority index to review their significance with regard to psoriasis, PsA, and other immune-mediated diseases.

Gene set enrichment analysis (GSEA)

To determine whether lists of prioritized genes output from Pi are enriched in targets with known or putative disease significance based on current evidence, we used an approach similar to the one used by Fang et al.[15] to evaluate the enrichment of 'gold standard' drug targets and disease signatures in our list of prioritized genes. All public database queries were performed on April 13th, 2021.

For PsA, we queried the ChEMBL database for a list of all current therapeutics for PsA (MeSH term D015535) and annotated the resulting 12 drugs currently in Phase III with their currently known drug target(s) (Supplementary Table 2). A list of upregulated and downregulated genes reported for PsA by a single study was also obtained from the CREEDS database (https://maayanlab.cloud/CREEDS).[20,21]

For psoriasis, drug targets were obtained directly from the Fang et al. study and filtered to include only those corresponding to Phase III drugs. From the CREEDS database, we obtained disease signatures of 10 datasets from 8 studies in humans and merged them into a single list of unique genes.

Drug target and disease signature lists for the combined analysis of psoriasis and PsA were obtained by taking the respective unions of all drug target lists as well as all disease signature lists described above.

In each of the above analyses, the drug target and disease signature lists, along with the priority rank information generated in this study by Pi, were input to the 'fgseaSimple' function of the *fgsea* 1.16.0 R package to perform GSEA using 20,000 permutations. Benjamini-Hochberg adjustment was then applied to the resulting p-values.

Results and Discussion

By utilizing psoriasis, PsA, and combined psoriatic diseases GWAS data as inputs for Pi, we were able to assign priority index scores to ~15,000 genes using genomic and annotation predictors, determine pathways most significantly enriched for highly prioritized targets, and identify potential nodes of intervention by both determining crosstalk between these pathways and by maximizing the number of highly prioritized interconnecting genes. In this study, a potential node of intervention was systematically defined as any node within the network of prioritized genes with greater than six edges. This value was chosen based on the distribution of total edges per node within the network plot in which the nodes with greater than six edges made up ≤25% of the nodes within the network plots for psoriasis and PsA. Through Pi, we are able to discover highly prioritized genes that are likely associated to psoriasis and PsA as well as potential therapeutic targets that are currently not being explored extensively.

Psoriasis

When the psoriasis GWAS data was analyzed through Pi (Figure 1A), the distribution of Pi gene scores was as follows: score 4–5: 6 genes (0.04%); score 3–4: 51 genes (0.33%); score 2–3: 811 genes (5.32%); score 1–2: 2847 genes (18.66%); score <1: 11,543 genes (75.65%) (Supplementary Table 3). GSEA of these prioritized targets revealed significant enrichments in genes targeted by current Phase III psoriasis therapeutics (normalized enrichment score 1.329, p = 0.03) and in psoriasis-associated genes (normalized enrichment scores 1.156, p = 0.0001) among the higher-scoring targets. The highest ranked genes were *LCE3D* (late cornified envelope protein 3D), *ICAM1* (intercellular adhesion molecule 1), *LCE3A*, *ADRA1B* (α−1B adrenergic receptor), and *DES* (desmin) with respective Pi scores of 5, 4.84, 4.62, 4.50. and 4.49 (Figure 1A, Supplementary Table 3). Additionally, pathways most significantly enriched for highly prioritized targets included interferon signaling, interleukin signaling, mobilization of lymphoid cells, cytokine signaling, Class I MHC (major histocompatibility complex)-mediated pathways, and adaptive and innate immunity (Figure 1B, Supplementary Table 4). These pathways fit into our current understanding of the pathogenesis of psoriasis.

We selected the top fifteen scored genes for further investigation within the biomedical literature. Based on the distribution of Pi gene scores, these genes have a Pi score range of 3.5–5 and make up less than 0.5% of all prioritized genes (Supplementary Table 3). Of these top fifteen genes, only those previously associated with psoriasis are discussed in order of Pi score. Of the highly prioritized genes, which include both GWAS seed and non-seed genes, all but *DES* have evidence from the literature supporting a biological association with psoriasis.

Late cornified envelope *(LCE) 3A, 3B, 3C*, and *3E* are protein coding genes that are expressed only in the epidermis and oral epithelia and involved in building structural proteins in the cornified envelopes of the stratum corneum.[22,23] These coding sequences have been highly conserved across mammals and are associated with skin tissue repair, initiating immune response to bacterial antigens and reshaping cutaneous antimicrobial activity. Because they are expressed when there is an injury to the skin, *LCE3* group gene deletion could affect skin barrier repair and susceptibility to developing psoriasis.[24] *LCE3A* was previously found to be significantly associated with psoriasis.[25,26] *LCE3B* and *LCE3C* genes are regulated by psoriasis-associated Th1 and Th17 cytokines, and the deletion of these two genes is associated with increased risk to develop psoriasis.[22,27] *LCE3B/C*-del is also significantly associated with increased expression of the upstream *LCE3A* gene in human skin.[25] Although strongly associated to psoriasis, further studies are needed to identify which therapies psoriasis patients with *LCE3* gene deletions respond best to.

Intracellular Adhesion Molecule 1 (*ICAM1*) encodes for a protein expressed on immune and endothelial cells.[28] It is thought to primarily mediate proinflammatory pathways through recruitment of immune cells and promotion of transendothelial migration of T lymphocytes into the dermis.[29,30] In addition to its association with psoriasis, *ICAM1* has also been associated with vascular morphologic changes and cardiovascular disease, which strengthens the link between cardiovascular comorbidities and psoriasis.[30,31] These vascular changes such as vasodilation, lengthening vessels, and increased expression of adhesion factors

such as *ICAM1* also aid in maintaining the inflammatory process in psoriasis.[32,33] *ICAM1* was a drug target of a previously marketed agent, efalizumab. Efalizumab (Raptiva®) is a recombinant humanized monoclonal antibody which inhibits the interaction of ICAM-1 with lymphocyte function-associated antigen-1, leading to T cell hyporesponsiveness.[34] Ultimately, efalizumab was removed from the drug market in 2009 after the observation of progressive multifocal leukoencephalopathy (PML) in several patients.[35] Although prior studies show its association to psoriasis, future systemic agents targeting *ICAM1* may be limited due to the known complications observed with prior inhibition of ICAM interactions leading to impaired adaptive antiviral immunity.[35]

ADRA1B encodes for the α−1B-adrenergic receptor which is involved in signaling by G-protein-coupled receptor (GPCR) and activation of cAMP-dependent protein kinase A (PKA) which could be important in psoriasis pathogenesis. Studies have shown that *ADRA1B* gene variants contribute to psoriasis in the Chinese population and also discovered a stronger association with psoriasis patients in the moderate-to-severe group.[36] Additionally, *ADRA1B* has been found to have prognostic value for papillary thyroid carcinoma and gastric carcinoma.[37,38] Adenosine was identified as a compound which modulates the effects of adrenoreceptors, and certain medications utilized in the treatment of psoriasis affect concentrations of adenosine, such as methotrexate.[39] However, there are limited studies evaluating how *ADRA1B* variants in patients affect responses to these medications, identifying an area of potential research. Of note, the priority index identified *ADRA1B* as a gene with a strong association with PsA as well, however, limited clinical data is currently available on the significance of this association and further research is needed.

The NF-kB Pathway Inhibitor *(NFKBIA)* gene encodes for a protein involved in the inhibition of NF-kB pathway. NF-kB is pivotal in the regulation of several biological processes, and its deregulation has been implicated in the immunologic pathways of several pathologies, including psoriasis, arthritis, and cardiovascular disease.[40] Psoriatic skin has been shown to have increased amounts of NF-kB, identifying it as a key mediator between immunity and keratinocyte dysregulation. Cytoplasmic inhibitors, including NFKBIA, bind to the NF-kB complex and prevent its translocation to the nucleus, inhibiting the downstream production of several transcriptional products central to psoriasis and psoriatic arthritis, including TNF-α. Studies have shown that a significant difference exists in *NFKBIA* between psoriatic arthritis and cutaneous psoriasis in the Chinese population, elucidating it as a possible genetic differentiator between manifestations of psoriasis.[41] Studies have examined how patients with *NFKBIA* respond to certain psoriasis medications. Patients with certain *NFKBIA* SNP variants have been noted to experience a poor response to ustekinumab while other variants near *NFKBIA* were found to have no role in predicting treatment response to etanercept.[42,43]

Reversionless 3-like (*REV3L*) is a protein encoding gene for a catalytic subunit of the DNA polymerase ζ (zeta), which plays an important role in the DNA damage tolerance mechanism.[44,45] It plays a role in homologous recombination, cell-cycle control, genomic stability, and somatic hypermutation.[46] Deletion of *REV3L* gene in mouse epidermis results in impairment of wound healing and subsequent proliferation of the epidermis.[47]

Mutations of *REV3L* are associated with rheumatoid arthritis in African populations.[48] Inhibition of REV3 has also been studied as an adjuvant therapy for the treatment of chemotherapy-resistant malignancies; however, it has yet to be explored as a therapeutic target for psoriasis.[49]

Leucyl and cystinyl aminopeptidase (*LNPEP*) encodes for a protein that cleaves peptide hormones. An analysis of the GEO database demonstrated that *LNPEP* gene expression was significantly downregulated in skin biopsies taken from involved psoriatic skin when compared to uninvolved skin in psoriasis patients and to the skin from healthy controls.[50] This downregulation suggests LNPEP could have a role in the pathologic process within psoriatic lesions, but further research exploring these implications are necessary. LNPEP is also an essential component of the renin-angiotensin system, which is known to be associated with both diabetes and cardiovascular disease.[50] Additionally, LNPEP was identified as a receptor for angiotensin IV, which activates NF-kB and other proinflammatory factors leading to possible downstream vascular damage.[51] This evidence further supports the potential involvement of LNPEP in the etiology of psoriasis, as well as provides a possible genetic link behind the complex relationship between psoriasis, cardiovascular disease, and diabetes.[50] Again, identifying which psoriasis therapies patients with this deletion respond to best is important given the possible role of LNPEP in the development of severe cardiovascular comorbidities.

Potential nodal points of interventions—Pi then identified potential nodes of intervention through determining crosstalk between these pathways and by maximizing the number of highly prioritized interconnecting genes. This process identified *IFNAR2, IFNGR1, TYK2, IL23A, IL23R, IL12B, STAT3, PIK3R1, IFNGR2, TNNT2, TNNI3, RELA, AKT1,* and *FOXO1* as potential nodes of intervention (Figure 1C).

Of the highly interconnected network genes with high Pi rating, *TYK2* is a current drug target that is already being explored. TYK2 is a member of the JAK family and is involved in the JAK-STAT pathway which plays a significant role in intracellular cytokine signaling, making it an integral part of psoriasis pathogenesis. Current TYK2 inhibitors include BMS-986165, PF-06826647, and Brepocitinib which are small molecule agents that can be administered orally or topically.[52] BMS-986165 a selective TYK2 inhibitor that is undergoing four Phase III clinical trials for psoriasis and PsA (NCT03624127, NCT03611751, NCT04036435, NCT03924427), and its results from the previous trials are encouraging.[53] PF-06826647 is another selective TYK2 inhibitor that is being tested in an ongoing Phase II trial for moderate-to-severe psoriasis (NCT03895372). Brepocitinib, formerly known as PF-06700841, is a potent TYK2/JAK1 inhibitor that has shown promise in the Phase I and II clinical trials for moderate-to-severe psoriasis.[54,55] Currently no other clinical trials with oral brepocitinib in psoriasis are ongoing; however, a Phase II trial for brepocitinib topical cream in mild-to-moderate psoriasis is in progress (NCT03850483).[52] The identification of the current drug target TYK2 helps support the relevance of the identified targets, especially given the reported efficacy and safety of these anti-TYK2 drugs.[52]

Other highly interconnected network genes are *IL23A, IL23R,* and *IL12B. IL23A* encodes for the IL-23p19 subunit of the IL23 cytokine which is currently a drug target of many IL-23 inhibitors. These include monoclonal antibodies such as guselkumab, tildrakizumab, and risankizumab which are all FDA approved for psoriasis treatment. *IL23R* encodes for a unique portion of the IL-23 receptor complex. While this specific gene is not a drug target, there are many IL-23 inhibitors that target the IL-23p19 subunit of the cytokine. The rationale behind selectively targeting IL-23 through inhibition of the IL-23p19 subunit was to increase its safety by maintaining the IL-12-mediated Th1 response to pathogens while still providing the same efficacy as IL-12/23p40 inhibitors.[56,57] Interestingly, *IL12B,* which was another potential node of intervention, encodes for this IL-12p40 subunit. The IL-23 receptor is composed of two parts: IL-12Rβ1, which is common with IL-12, and IL-23R which is specific for IL-23. Because IL23R is unique to IL23 whereas IL-12Rβ1 is not, it could be worth further investigating IL23R as a potential drug target. Similarly, Pi identified interferon α and β receptor subunit 2 (*IFNAR2*) as a potential node of intervention; however, previous evidence supports the use of type I IFNs, the ligand of IFNAR, as a potential therapeutic target and not the receptor itself.[58] Prior studies suggest that targeting type I IFNs combined with T cell therapy could result in a sustainable treatment for psoriasis, especially for patients with paradoxical psoriasis skin lesions which have an overexpression of type I interferons compared to classical psoriasis lesions.[59,60]

Many of the other highly interconnected network genes with high Pi rating are not currently being studied as drug targets; however, previous evidence supports their involvement in psoriasis pathogenesis: *IFNAR2, IFNGR1, PIK3R1, IFNGR2, TNNT2, TNNI3, RELA, AKT1,* and *FOXO1.* Given Pi's aforementioned success in identifying current drug targets, it would be worth exploring the clinical value of these genes as potential drug targets.

Psoriatic Arthritis

Pi has not yet been previously used to examine PsA. Given the sparse PsA specific genetic studies and PsA specific drug targets, we conducted an analysis using PsA GWAS data. When the PsA GWAS data was analyzed through Pi (Figure 2A), the distribution of Pi gene scores was as follows: score 4–5: 4 genes (0.03%); score 3–4: 187 genes (1.23%); score 2–3: 716 genes (4.72%); score 1–2: 3199 genes (21.07%); score <1: 10,646 genes (72.95%) (Supplementary Table 5). These prioritized genes were significantly enriched in targets of Phase III PsA drugs (normalized enrichment score 1.394, $p = 0.008$) as well as genes reported by a previous transcriptomic study of PsA to be associated with disease (normalized enrichment scores 1.184 and 1.229 for up- and downregulated genes, $p < 0.001$).[20] The highest ranked genes were *ADRA1B*, *POU5F1* (transcription factor for embryonic development), *TTC1* (Tetratricopeptide Repeat Domain 1), *MCCD1* (Mitochondrial Coiled-Coil Domain 1), and *UBLCP1* (Ubiquitin Like Domain Containing CTD Phosphatase 1) with respective Pi scores of 5, 4.64, 4.44, 4.07, and 3.92 (Figure 2A, Supplementary Table 4). Pathways most significantly enriched for highly prioritized targets included G protein-coupled receptors (GPCR) ligand binding and signaling, interleukin signaling, and cytokine signaling (Figure 2B, Supplementary Table 6). Interestingly, these pathways showed an overall stronger association to PsA than the pathways associated to psoriasis.

Similar to Pi results for psoriasis, the top fifteen scored genes for PsA have a Pi score range of 3.5–5 and make up less than 0.5% of all prioritized genes (Supplementary Table 5). Of these top fifteen genes, only those previously associated with PsA are discussed in order of Pi score. Several of the highest prioritized genes for PsA identified by Pi have literature associations with psoriasis, but not PsA, such as *ADRA1B, POU5F1, TTC1*, and *MCCD1*.[36,61,62] Interestingly, another highly prioritized gene *UBLCP1* has no current evidence supporting its association with psoriasis or PsA. *UBLCP1* (ubiquitin like domain containing CTD phosphatase 1) is a protein encoding gene for phosphoprotein phosphatase that acts on 26S nuclear proteasomes, which decreases their proteolytic activity. The dysregulation of the ubiquitin-proteasome system is associated with human diseases.[63] *UBLCP1* is predicted to be a gene target of the NF-kB1 transcription factor that leads to inappropriate immune cell development and delayed cell growth.[64]

C-C motif chemokine ligand 11 (*CCL11* or eotaxin-1) is an antimicrobial gene involved in both immunoregulatory and inflammatory pathways. CCL11 is produced in the presence of allergic inflammation and promotes both eosinophil and T cell recruitment, leading to a Th2 response.[65] While Th2 is typically thought to accompany allergic diseases such as atopic dermatitis, it was recently suggested that during chronic PsA there is a shift from the Th1 to the Th2 disease state.[66] While CCL11 was not suggested in the mechanism of this shift, it would be interesting to see if it has an impact on the disease progression of PsA, especially considering a study that noted that *CCL11* was significantly upregulated in the serum of patients with PsA when compared to healthy controls.[67] Currently, the exploration of CCL11 as a drug target is underway. An anti-eotaxin-1 monoclonal antibody, bertilimumab, is being investigated for bullous pemphigoid and recently completed Phase IIa clinical trials.[68] Future research is needed to explore the possibilities of bertilimumab or other agents which target the CCL11 pathway for the treatment of psoriatic arthritis.

Potential nodal points of intervention—The potential nodes of intervention identified for PsA in the network plot were *GNAQ*, *PLCB1*, and *GNA12* (Figure 2C). Interestingly, most of the highly interconnected network genes with high Pi rating indicated by the PsA network plot are involved in GPCR-mediated signaling, which is also identified as one of the strongest associated pathways in the pathway enrichment analysis. These gene nodes include G protein subunit α Q (*GNAQ*), phospholipase C-β1 (*PLCB1*), and G protein subunit α-I2 (*GNAI2*). GNAQ has previous evidence supporting its role in Th17 cell differentiation and cytokine production in psoriasis pathogenesis but not specifically in PsA development.[69] GNAQ couples with a seven-transmembrane receptor to activate PLCB1, and there is evidence that PLCB1 is differentially expressed in PsA patients and that it is associated to chemokine signaling.[70,71] *GNAI2* has also been shown to have reduced expression in PsA patients.[72] GPCRs work by inducing downstream intracellular signaling in response to ligand binding, and these signaling pathways can yield various physiological results. Previous evidence also supports GPCR involvement in the pathogenesis of PsA as seen with C-C chemokine receptor 4 (CCR4), a G_i protein, and sphingosine 1-phosphate receptor 1 (S1PR1), which couples with G_i proteins to initiate signaling.[73] GPCRs are common drug targets for a variety of diseases and components of the GPCR pathway are currently being explored as a therapeutic target for autoimmune diseases such as PsA, rheumatoid arthritis,

and psoriasis.[73,74] Given the vast variety of G proteins and associated molecules, Pi aids in narrowing the selection of drug targets that are most likely to provide the greatest efficacy.

Combined Psoriatic Diseases

When the combined psoriatic disease GWAS data was used as input for Pi, the highest ranked genes were very similar to those from the psoriasis GWAS data (Table 1, Figure 3A, Supplementary Table 7), and GSEA also indicated a significant enrichment of drug targets (normalized enrichment score 1.360, $p = 0.005$) and disease signatures (normalized enrichment score 1.158, $p = 10^{-4}$) among higher-ranked genes. The strongest associated pathways were also very similar to those from the psoriasis GWAS data (Figure 3B, Supplementary Table 8). While the major nodal points of intervention are very similar to those seen in the psoriasis network plot, the combined psoriatic disease data yielded a more complex network plot that has more interaction between these nodes (Figure 3C).

Conclusions

Psoriasis and psoriatic arthritis have been associated with >100 genetic variants, of which only a minority have previously been associated with drug targets. Using Pi, we have identified several high-scoring novel genes that are exploratory targets for therapeutic intervention. While some of these targets have been examined in research studies (e.g., *ICAM1, NF-kB, REV3L, ADRA1B* for psoriasis; *CCL11* for PsA), others have not yet been investigated (e.g., *LNPEP, LCE3* for psoriasis; *UBLCP1* for PsA).

In addition, several nodal points of potential intervention were identified that are promising for future therapeutic targets. Of those identified, some targets are already being investigated as potential psoriasis drug targets such as *TYK2*, and others have yet to be explored including *PPP2CA, YAP1, PI3K, AKT, FOXO1, RELA, CSF2, IFNGR1, IFNGR2* for psoriasis and *GNAQ, PLCB1, GNAI2* for PsA. Interestingly, *IL23R* and *IFNAR2* were also identified as potential nodes of intervention for psoriasis; however, their respective ligands are currently being explored as therapeutic targets. Based on these findings, follow up studies can be performed to study the efficacy of these novel potential drug targets.

The initial publication of Pi included data on psoriasis but the GWAS SNPs used did not include more recent studies included here. Moreover, Pi has not yet been used in a way that accounts for the distinction between psoriatic arthritis and psoriasis. Given the sparse PsA specific genetic studies and PsA specific drug targets, our analysis provides new insights. Through this research, we hope to contribute to drug discovery for psoriasis and psoriatic arthritis with the goal of ultimately improving patient care and patient satisfaction with treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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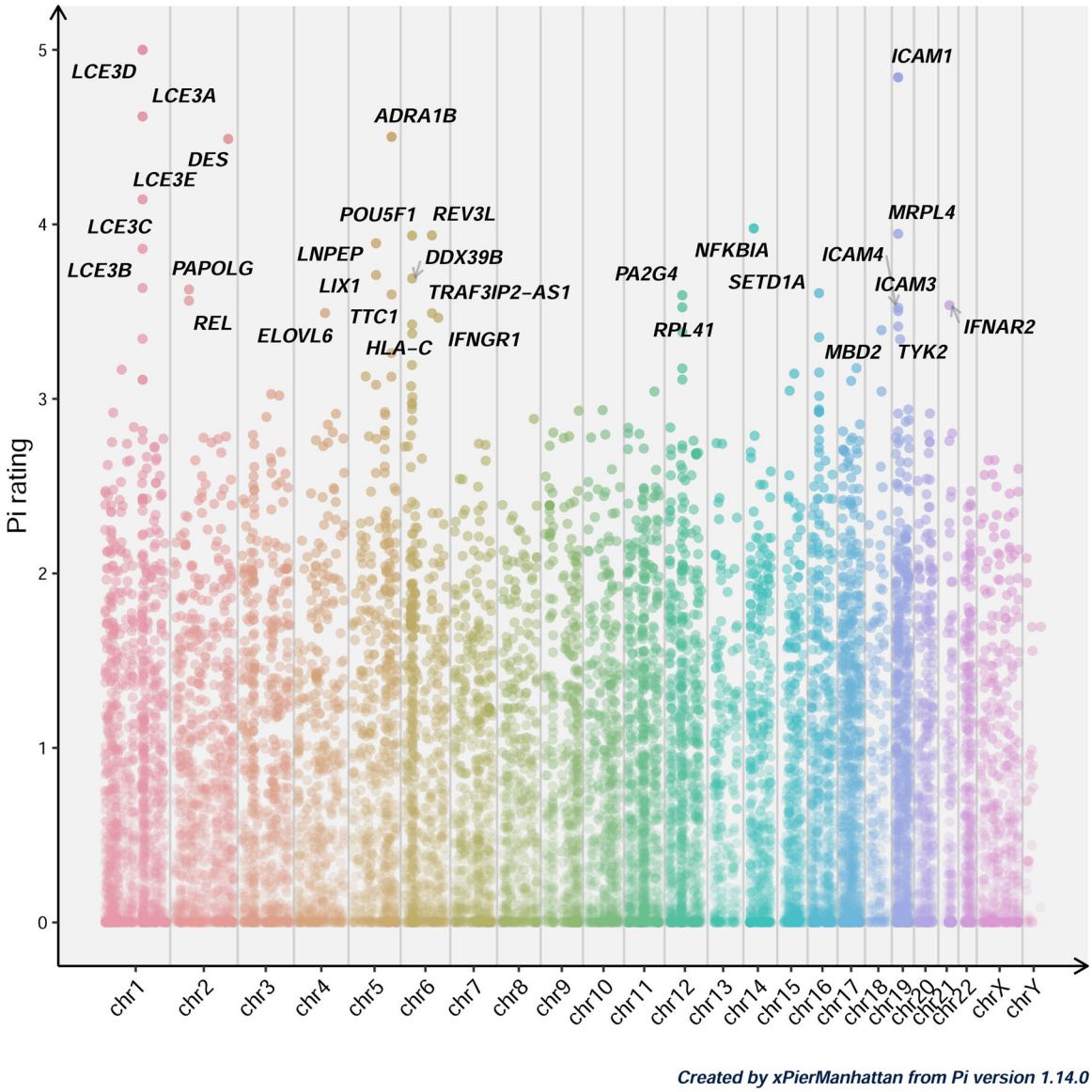
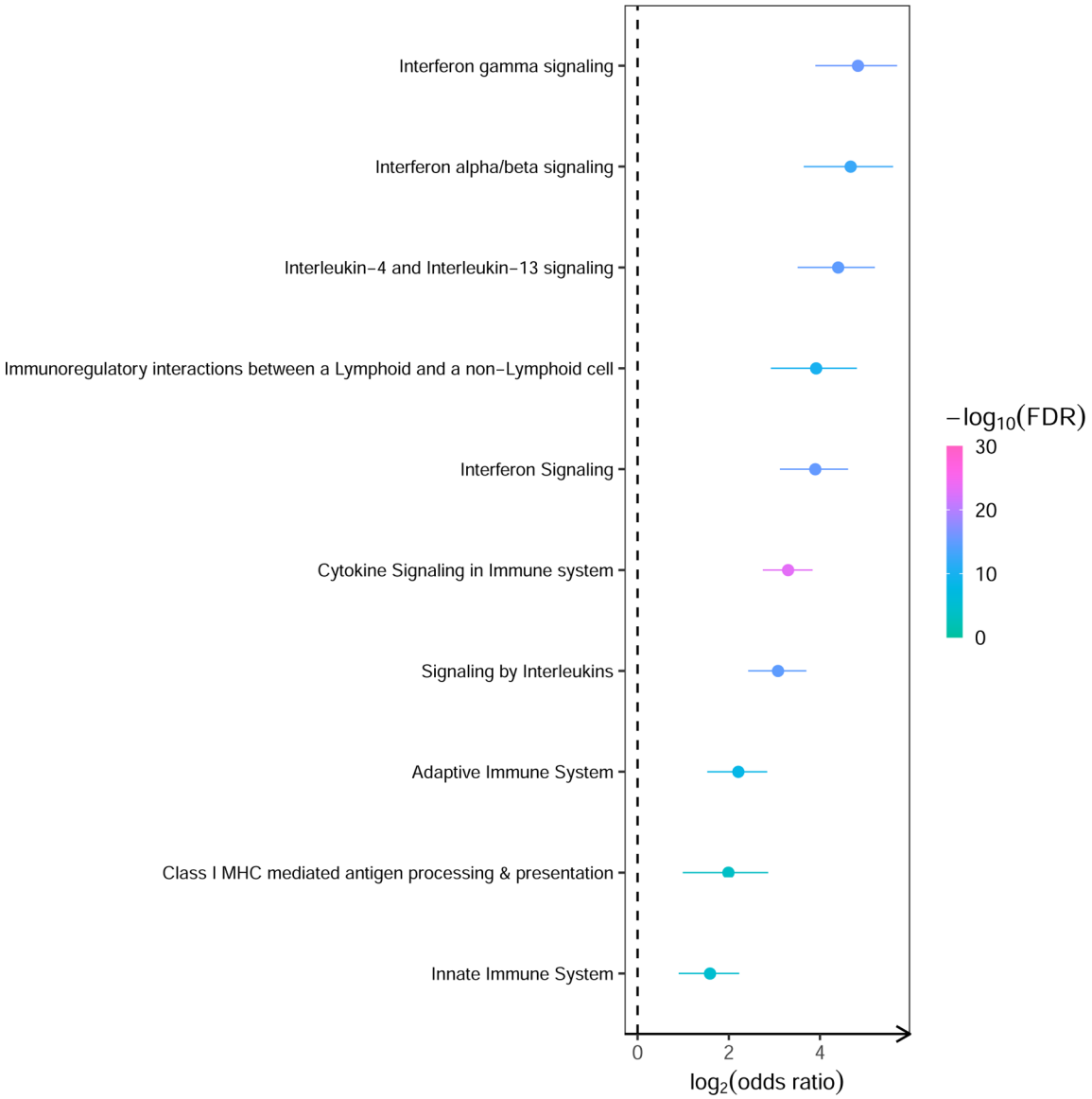




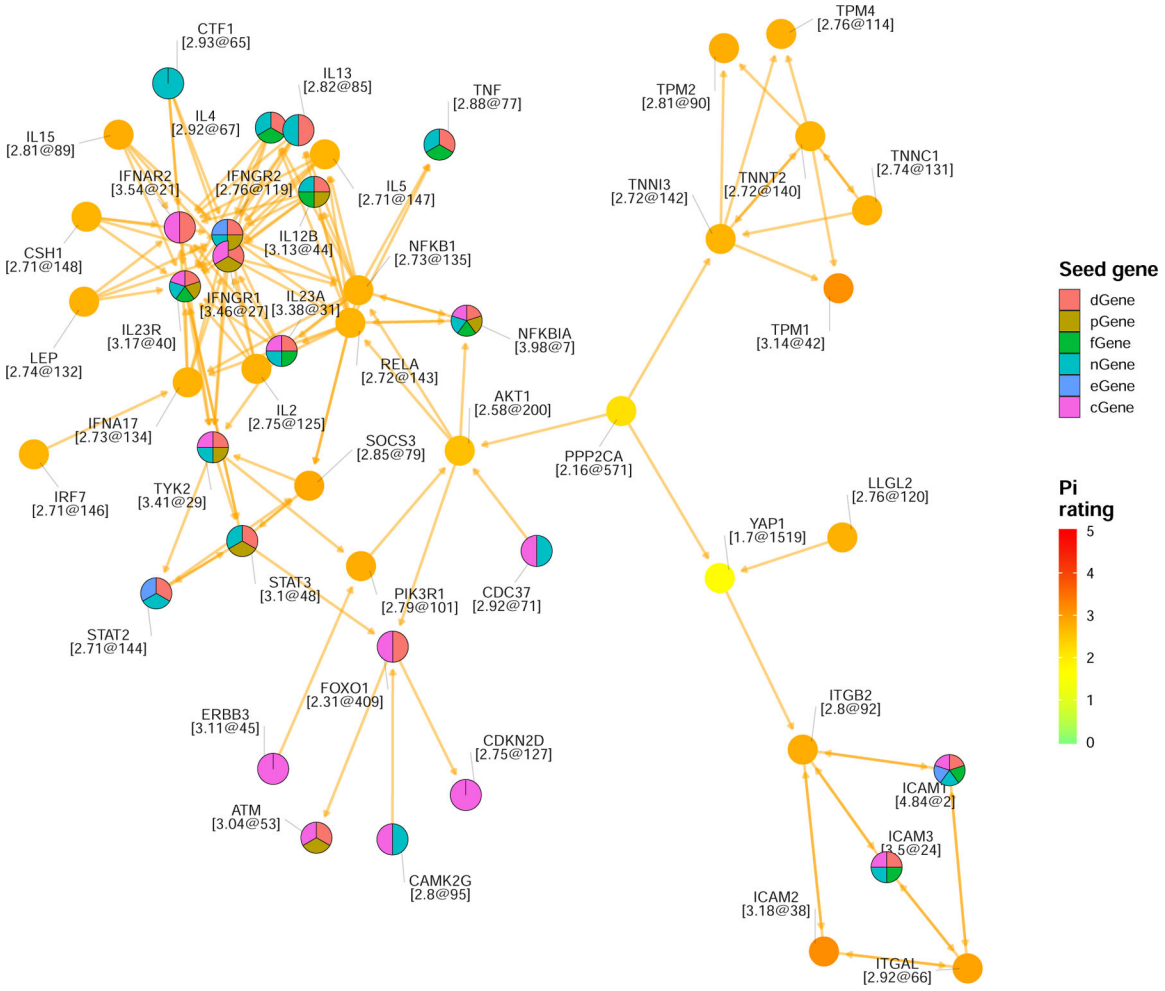
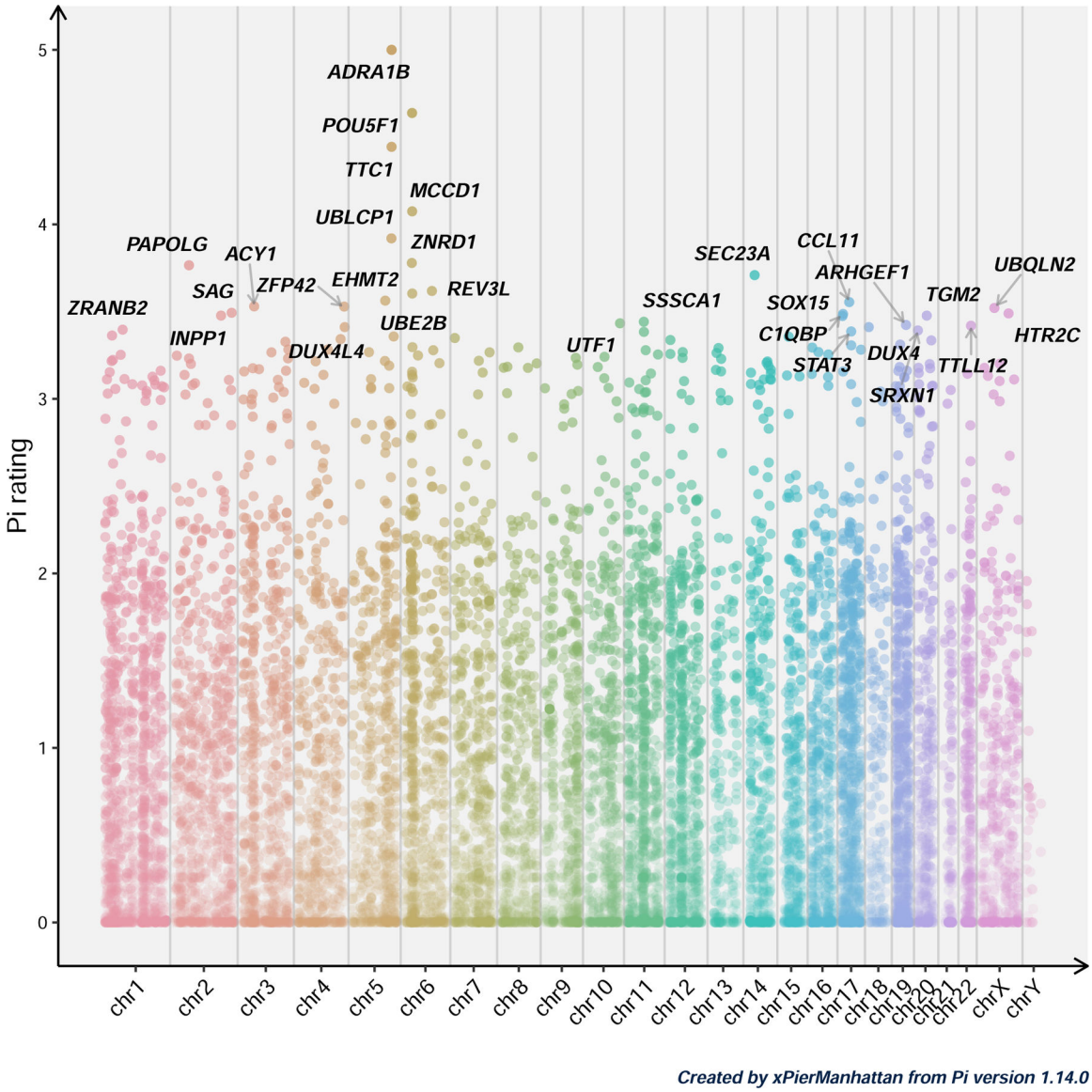
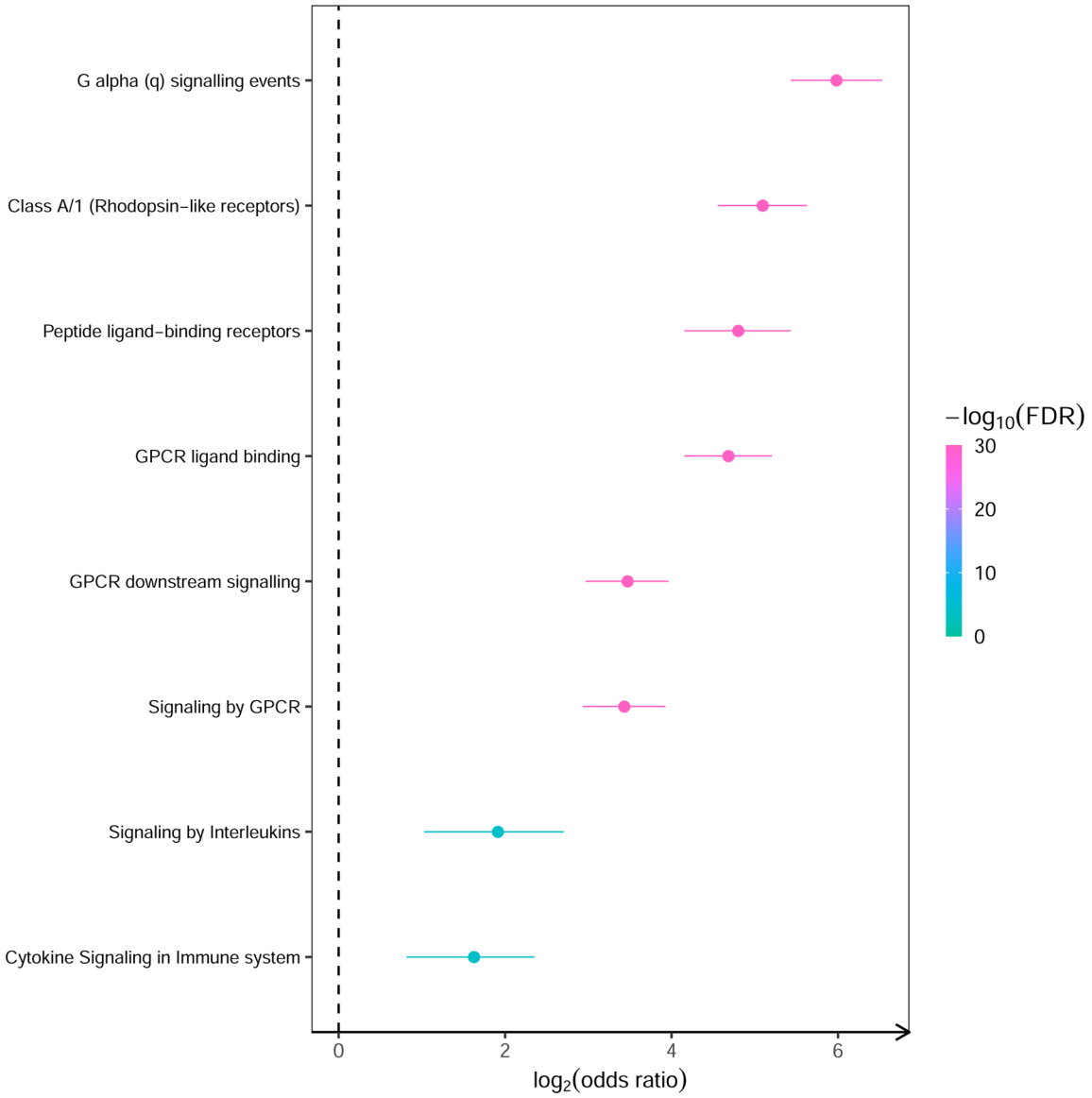


Figure 1. Pi applied to psoriasis.

A) Prioritized target genes for psoriasis in which the top 30 genes are named. Colors denote genomic location. Gray arrows indicate gene's corresponding data point. B) Prioritized target pathways for psoriasis based on top 1% (top 150) prioritized genes (sourced from REACTOME version 73). One-sided Fisher's exact test used to calculate (odds ratio) ORs with 95% confidence intervals (CIs; represented by lines). C) Network plot visualizing target pathway crosstalk for psoriasis, including evidence from associated genomic and annotation predictors. Node colors indicate Pi rating and evidence. Node labels indicate gene name, Pi score, and Pi ranking (i.e., ITGAM [3.28@59] has a Pi score of 3.28 and is ranked 59). Arrows indicate direction of relationship.





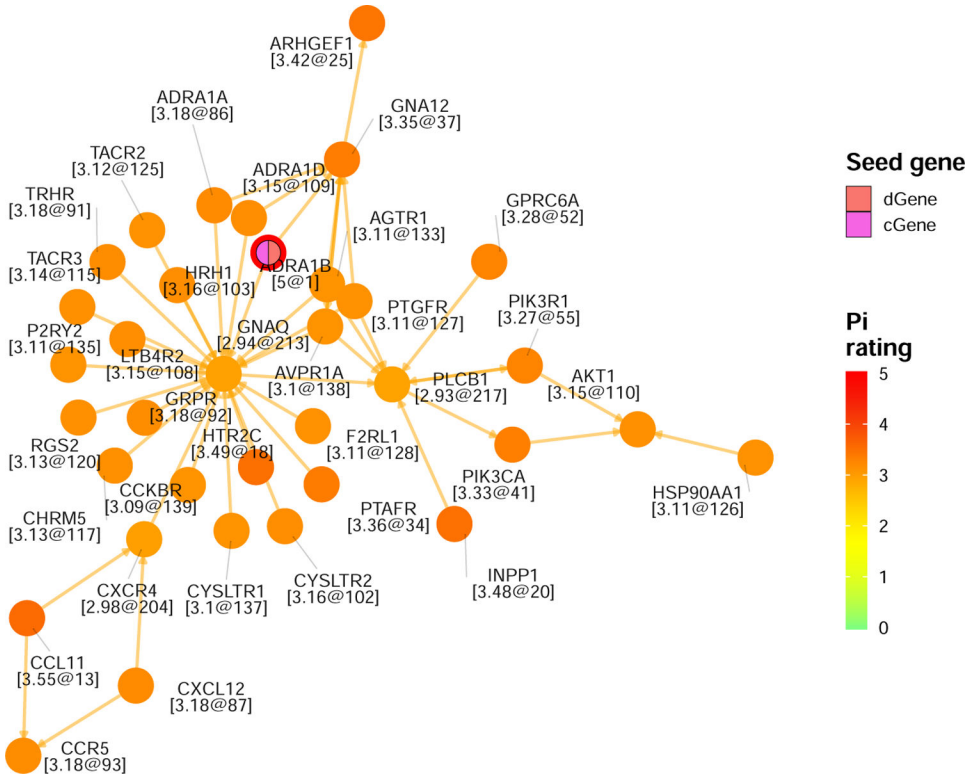
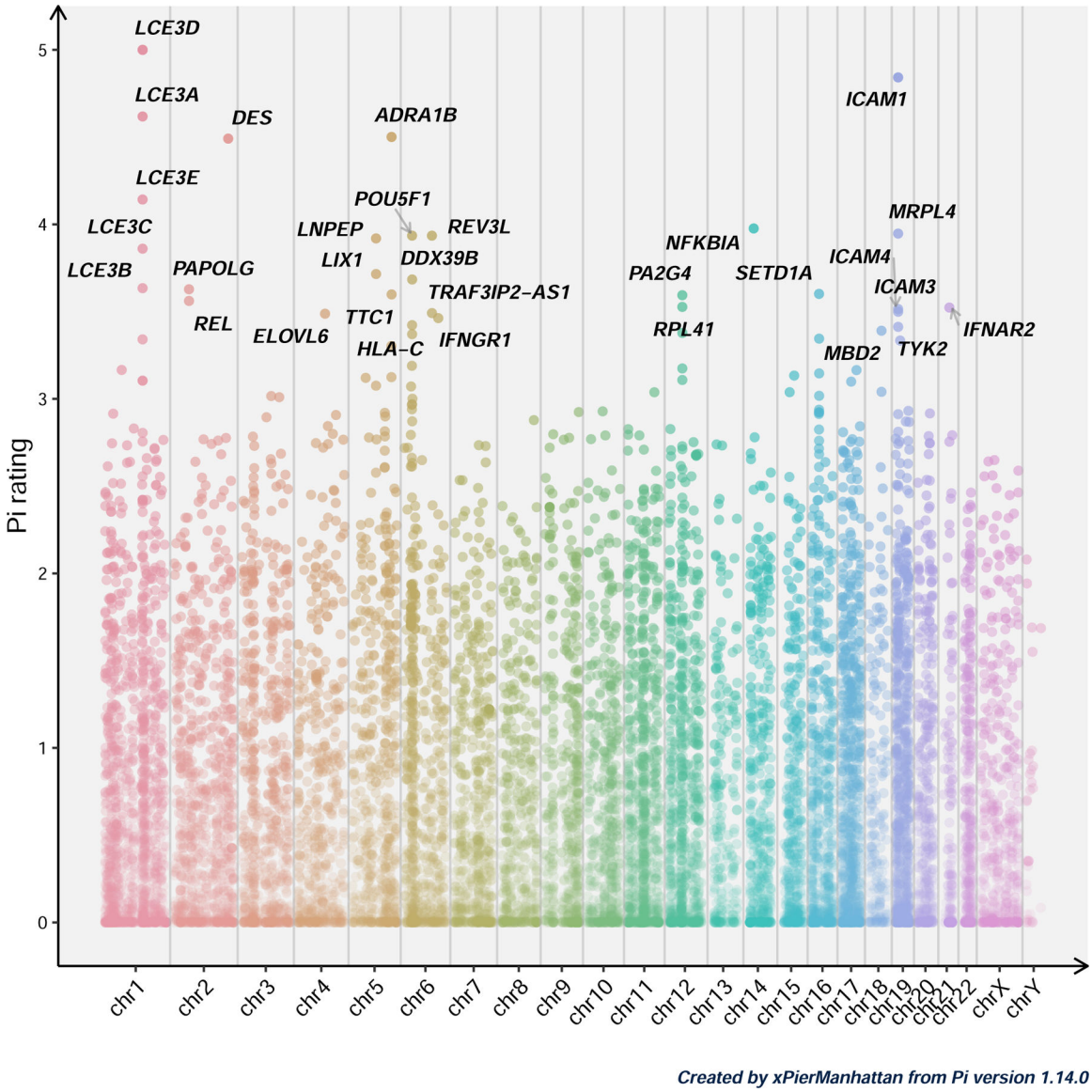
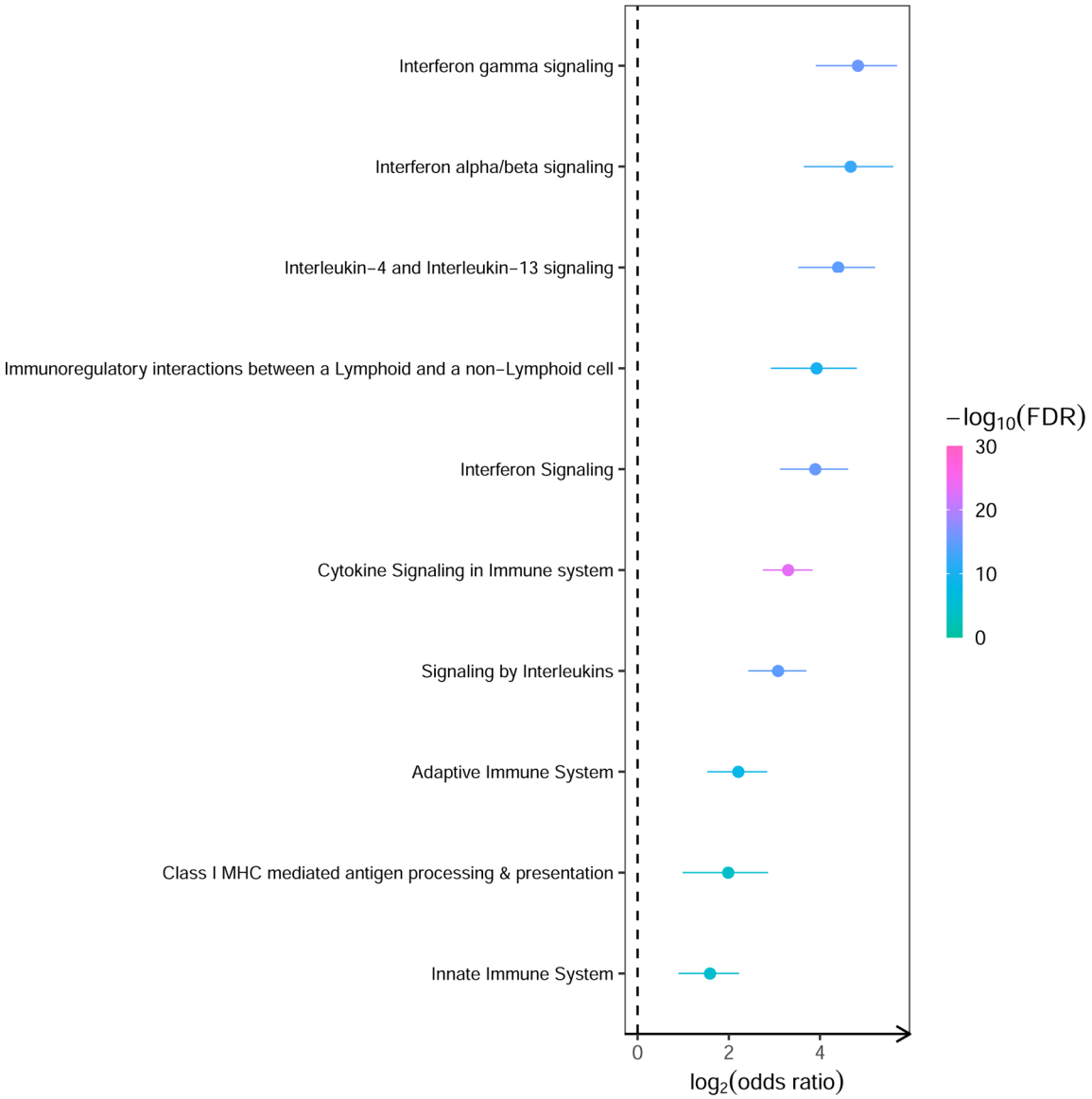


Figure 2. Pi applied to psoriatic arthritis shows unique results compared to psoriasis.

A) Prioritized target genes for psoriatic arthritis in which the top 30 genes are named. Colors denote genomic location. Gray arrows indicate gene's corresponding data point. B) Prioritized target pathways for psoriatic arthritis based on top 1% (top 150) prioritized genes (sourced from REACTOME version 73). One-sided Fisher's exact test used to calculate ORs with 95% CIs (represented by lines). C) Network plot visualizing target pathway crosstalk for psoriatic arthritis, including evidence from associated genomic and annotation predictors. Node colors indicate Pi rating and evidence. Node labels indicate gene name, Pi score, and Pi ranking (i.e., ITGAM [3.28@59] has a Pi score of 3.28 and is ranked 59). Arrows indicate direction of relationship.





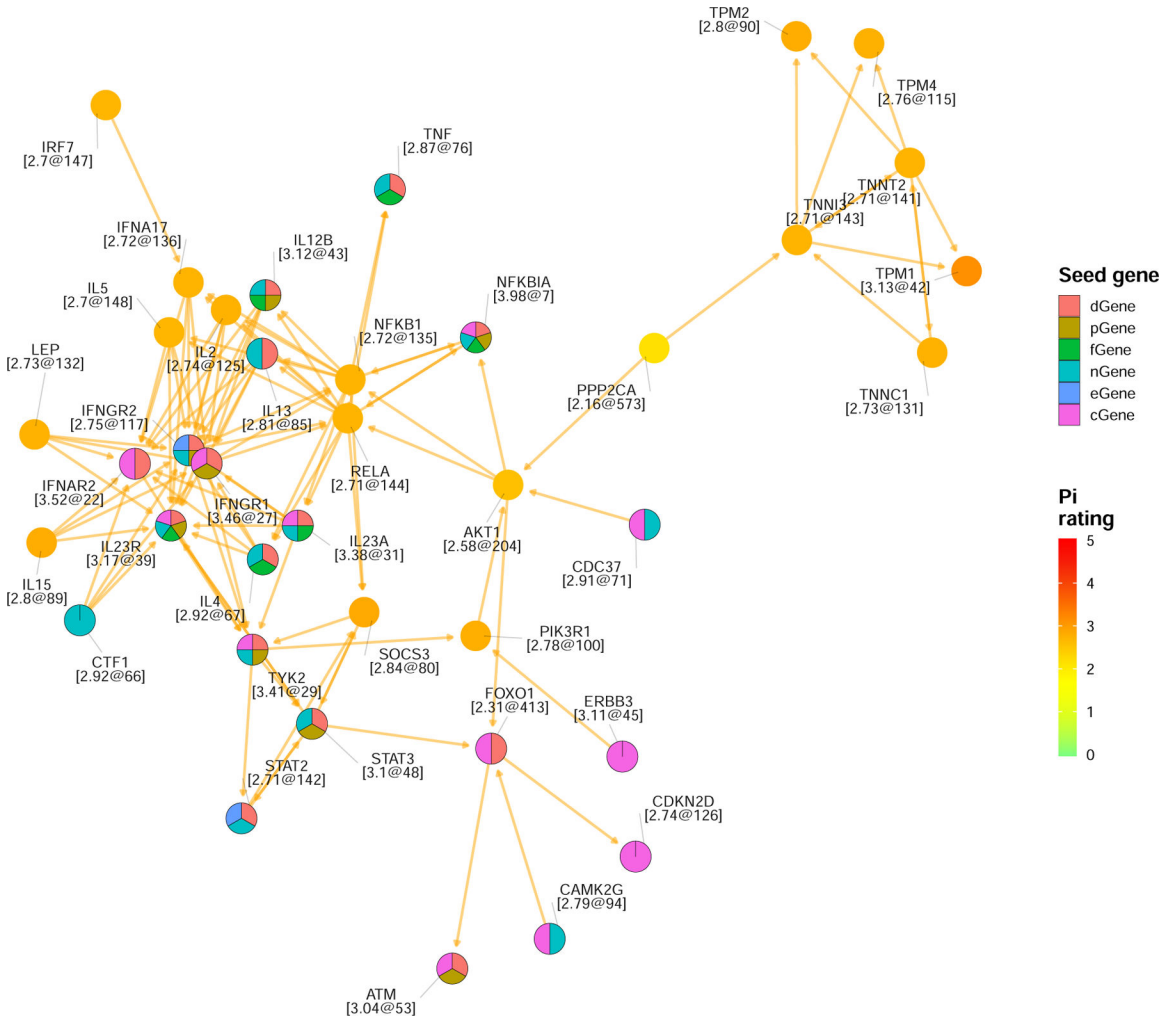


Figure 3. Pi applied to combined psoriatic diseases shows similar results to psoriasis.

A) Prioritized target genes for combined psoriatic diseases in which the top 30 genes are named. Colors denote genomic location. Gray arrows indicate gene's corresponding data point. B) Prioritized target pathways for combined psoriatic diseases based on top 1% (top 150) prioritized genes (sourced from REACTOME version 73). One-sided Fisher's exact test used to calculate ORs with 95% CIs (represented by lines). C) Network plot visualizing target pathway crosstalk for combined psoriatic diseases, including evidence from associated genomic and annotation predictors. Node colors indicate Pi rating and evidence. Node labels indicate gene name, Pi score, and Pi ranking (i.e., ITGAM [3.28@59] has a Pi score of 3.28 and is ranked 59). Arrows indicate direction of relationship.

Table 1.

Summary of results between disease groups.

Disease	Analysis	Gene Name	Rank	Pi Score	Currently targeted pathway for associated disease	Reference
PSO	High-Scoring Genes	*LCE3D*	1	5	N	
		ICAM1	2	4.84	Y	Guttman-Yassky et al. 2008[34]
		LCE3A	3	4.62	N	
		ADRA1B	4	4.5	N	
		DES	5	4.49	N	
	Potential Node of Intervention	*IFNAR2*	21	3.54	N	
		IFNGR1	27	3.46	N	
		TYK2	29	3.41	Y	Nogueira et al. 2020[52]
		IL23A	31	3.38	Y	Fotiadou et al. 2018[56]
		IL23R	40	3.17	Y	Fotiadou et al. 2018[56]
		IL12B	44	3.13	Y	Savage et al. 2015[57]
		STAT3	48	3.103097	Y	Miyoshi et al. 2011[75]
		PIK3R1	101	2.79	N	
		IFNGR2	119	2.76	N	
		TNNT2	140	2.72	N	
		TNNI3	142	2.72	N	
		RELA	143	2.72	N	
		AKT1	200	2.58	N	
		FOXO1	409	2.31	N	
PsA	High-Scoring Genes	*ADRA1B*	1	5	N	
		POU5F1	2	4.64	N	
		TTC1	3	4.44	N	
		MCCD1	4	4.07	N	
		UBLCP1	5	3.92	N	
	Potential Node of Intervention	*GNA12*	37	3.35	N	
		GNAQ	213	2.94	N	
		PLCB1	217	2.93	N	
Combined Psoriatic Diseases	High-Scoring Genes	*LCE3D*	1	5	N	
		ICAM1	2	4.84	Y	Guttman-Yassky et al. 2008[34]
		LCE3A	3	4.62	N	
		ADRA1B	4	4.5	N	

Disease	Analysis	Gene Name	Rank	Pi Score	Currently targeted pathway for associated disease	Reference
		DES	5	4.49	N	
		IFNAR2	22	3.53	N	
		IFNGR1	27	3.46	N	
		TYK2	29	3.41	Y	Nogueira et al. 2020[52]
		IL23A	31	3.38	Y	Fotiadou et al. 2018[56]
		IL23R	39	3.17	Y	Fotiadou et al. 2018[56]
		IL12B	43	3.12	Y	Savage et al. 2015[57]
		STAT3	48	3.1	Y	Miyoshi et al. 2011[75]
	Potential Node of Intervention	*IL4*	67	2.92	Y	
		IL13	85	2.81	Y	
		IFNGR2	117	2.75	N	
		IL2	125	2.74	N	
		NFKB1	135	2.71	N	
		TTNT2	141	2.71	N	
		TNNI3	143	2.71	N	
		RELA	144	2.71	N	
		IL5	148	2.7	N	
		AKT1	204	2.58	N	
		FOXO1	413	2.31	N	