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REVIEW ARTICLE

Psoriasis and Genetics

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Psoriasis is a common inflammatory skin disease caused by the interplay between multiple genetic and environmental risk factors. This review summarises recent progress in elucidating the genetic basis of psoriasis, particularly through large genome-wide association studies. We illustrate the power of genetic analyses for disease stratification. Psoriasis can be stratified by phenotype (common plaque versus rare pustular variants), or by outcome (prognosis, comorbidities, response to treatment); recent progress has been made in delineating the genetic contribution in each of these areas. We also highlight how genetic data can directly inform the development of effective psoriasis treatments.

Key words: psoriasis; genetics; precision medicine; disease progression; treatment outcome.

Dermatological research has made extraordinary progress over the past 100 years. This has been matched – if not exceeded – by advances in the field of genetics, particularly in the two decades since the initial mapping of the human genome (1, 2). Recent insights into the genetic basis of the common skin disease psoriasis illuminate the translational potential of genetic studies, having directly informed the design of several powerful biologic therapies and small molecule inhibitors.

Psoriasis is a chronic immune-mediated inflammatory disease that affects around 2% of the world's population (3). It has been designated a serious non-communicable disease by the World Health Organisation and its increasing prevalence represents a substantial global public health burden (4). Genetic research has delivered critical insights into the biology of psoriasis. We now know that psoriasis is a multifactorial disease caused by the interplay between multiple inherited alleles (**Box 1**) and environmental risk factors. Indeed, it has a particularly strong genetic component among complex diseases, with heritability estimated to exceed 60% (5).

Unlike other biological features, the genome is fixed at birth and does not vary by cell or tissue type, or in response to stimuli: in this sense it reveals the causal

SIGNIFICANCE

Psoriasis has benefited greatly among dermatological conditions from genome-wide association studies (GWAS) of increasingly large, clinically well-described samples. Sixty-five regions of the genome have been linked to psoriasis risk in Europeans, with the largest contribution due to *HLA-C*06:02*, a variant of an important gene involved in immunity. Other regions implicate numerous immune and skin barrier processes in psoriasis development. Recent GWAS-based research has shown that genetics can help distinguish subgroups of psoriasis patients characterised by type (pustular vs. plaque psoriasis), development of joint disease or response to various drugs. This may help inform future tailored treatment strategies for individuals with psoriasis.

biology of psoriasis. In this review, we describe how genetic studies have helped to disentangle pathogenic mechanisms of psoriasis and informed the selection of therapeutic targets. We also highlight the potential of genetic biomarkers as a stratification tool for the effective clinical management of psoriasis.

GENETICS OF PLAQUE PSORIASIS

Early genetic findings

It has long been observed that the incidence of psoriasis is significantly higher among first- and second-degree relatives of sufferers than the general population (6, 7), and it is more concordant among monozygotic than dizygotic twins (8–10).

Linkage studies identified at least 9 genomic regions (loci) that co-segregated with psoriasis (*PSORS1-9*) in multiplex pedigrees. However, most of these findings could not be replicated, which underscores the limitations of linkage approaches for the analysis of multifactorial conditions (11). A notable exception is the *PSORS1* region, which maps to the class I interval of the major histocompatibility complex (MHC) that primarily encodes genes involved in antigen presentation (12–14). The region also contains the candidate gene corneodesmosin (*CDSN*), which encodes a desmosomal protein involved in keratinocyte cohesion and desquamation (15). *PSORS1* has the largest effect size and accounts for 35–50% of disease heritability explained by known

Box 1 – Genetic terminology

Alleles: Alternative variants of a gene (or other segment of DNA).

Single nucleotide polymorphism (SNP): A DNA sequence change affecting a single genomic position.

Linkage disequilibrium (LD): Genetic variants are in LD if they are in close proximity on the same chromosome and therefore less likely to be separated by recombination during meiosis, tending to be inherited together and being correlated in the population.

Susceptibility loci: Genomic regions that contain variants showing statistically significant association in a disease susceptibility GWAS (usually more than one variant due to LD).

Imputation: The statistical ascertainment of an individual's probable genotype at known genetic variants that exist in between markers genotyped on a GWAS chip. This requires large panels of reference genomes in which genotypes are available for the "missing" variants.

Polygenic risk score (PRS): A composite measure of genetic risk for a disease. Once a susceptibility GWAS has been completed, the polygenic risk for any genotyped individual (who may not have been included in the original GWAS) can be calculated by summing the number of risk alleles they carry at each susceptibility locus (usually weighted by the effect size observed at that locus).

Genetic correlation: The degree to which the genetic influences on two different traits are similar.

Mendelian randomisation: An approach to assess how far one trait (typically representing a modifiable exposure) is causal of another trait (typically a health outcome) by estimating the effects of genetic variants associated with the first trait on the second.

Next-generation sequencing: High-throughput and highly parallelised DNA sequencing, typically of the whole genome or exome (the protein coding portion of the genome).

loci. Despite the complex correlation structure across the MHC due to extensive linkage disequilibrium (Box 1) (16), *HLA-C*06:02* is now confidently considered the most likely causal susceptibility allele, since single nucleotide polymorphisms (SNPs; Box 1) that tag this allele have generated the most significant association signals in subsequent case-control studies (17, 18). Fine mapping studies have suggested the presence of additional association signals within *PSORS1*, some of which are population-specific (19–22).

The only other successfully validated linkage results are the *PSORS2* and *PSORS4* loci on chromosomes 17q25 and 1q21, respectively. The most likely susceptibility gene in *PSORS2* is *CARD14*, which encodes a nuclear factor-κB (NF-κB) activator and harbours variants associated with rare and common forms of psoriasis (23–25). *PSORS4* contains the late cornified envelope (LCE) genes, which encode stratum corneum proteins involved in terminal epidermal differentiation. This locus has been implicated in psoriasis susceptibility in genome wide association studies of both European and Chinese populations (26, 27).

Psoriasis in the GWAS and post-GWAS era

Genome-wide association studies (GWAS) use highly optimised microarrays that can efficiently and robustly genotype several million genetic markers across the genome. With sufficiently large sample numbers, GWAS allows even small differences in allele frequencies between disease cases and unaffected controls to be detected, making it a much more powerful approach than linkage analysis. As such, GWAS have fundamentally changed the genetic dissection of common complex diseases such as psoriasis. By 2010, initial GWAS efforts in psoriasis

had identified 21 susceptibility loci in Europeans (17, 18, 28, 29).

One inherent limitation of GWAS, however, is that it only uncovers statistical relationships. The genetic variants identified by GWAS may actually, by virtue of linkage disequilibrium, be tagging a separate 'causal' variant that exerts a biological effect and modifies disease risk. To refine GWAS signals and thus identify potential causal susceptibility alleles, genotyping arrays with dense coverage in regions of interest have been employed. The immunochip included 200,000 SNPs focused in known susceptibility loci for a range of immune-mediated diseases (30). In psoriasis, meta-analysis of immunochip data almost doubled the number of known susceptibility loci and uncovered candidate causal variants at 10 loci including in the innate immunity genes *DDX58* and *CARD14* (31).

More recently the exome chip aimed to comprehensively genotype protein-altering variants, including rare variants. Exome chip meta-analysis of 12,000 psoriasis cases and 29,000 controls highlighted potential functional SNPs within 11 known psoriasis susceptibility loci. This study provided novel insights into the complex role in psoriasis susceptibility of rare variants in the type I interferon signalling genes *IFIH1* and *TYK2* (32).

Rather than physically genotyping additional SNPs that are not included in GWAS arrays, however, it is becoming standard practice to perform genome-wide imputation (Box 1) using freely-available computational resources (33, 34). Imputation has been critical in facilitating the larger psoriasis meta-analyses, which combine data generated by different GWAS platforms (35–37). Indeed, an improved imputation strategy revealed a novel psoriasis susceptibility locus at *DLEU1*, linked to apoptosis, in previously analysed GWAS data (37).

Finally, combining datasets from international collaborations in meta-analyses of genome wide association studies has been essential to enhance statistical power and uncover novel disease susceptibility loci (18, 28, 29, 31, 38). A recent meta-analysis of psoriasis GWAS with a combined effective sample size of > 39,000 individuals identified 16 novel disease-associated regions (36).

PATHOGENIC INSIGHTS FROM GENETIC DISCOVERIES

As a result of GWAS, targeted association and meta-analysis efforts, the number of independent genomic loci contributing to susceptibility to common plaque psoriasis in populations of European ancestry now stands at 65 (32, 36, 37). More than 30 loci have been implicated in Han Chinese individuals (39). Although these susceptibility loci can span many genes, many of the lead SNPs lie in proximity to genes involved in specific adaptive and innate immune pathways. These include genes involved

in antigen presentation (*HLA-C, ERAP1*), T17 cell activation (*IL23R, IL23A, IL12B, TRAF3IP2*), innate antiviral immunity/type I interferon signalling (*RNF114, IFIH1*) and skin barrier function (*LCE3B/3D*) (**Fig. 1**) (17, 18, 26, 28, 40–42). The coding variants in genes such as *IL23R, TYK2* and *TNFSF15* uncovered by targeted association analyses further underscore the involvement of the interleukin (IL)-23/T17 axis in disease pathogenesis (31, 32, 38, 39, 43).

Genetic studies have thus provided important mechanistic insights into the aetiology of psoriasis, and support a pathogenic interplay between immune activation and disruption of skin barrier function (44). There is also evidence of gene-gene interactions (epistasis) contributing to disease heritability, since variants in *ERAP1* (encoding an enzyme that trims peptide antigens for loading onto MHC class I molecules) only confer disease susceptibility in individuals also harbouring the *HLA-C* risk allele (18). Once GWAS association summary statistics are in hand, there are several additional *in silico* approaches that can help to pinpoint relevant causal genes and variants before costly hypothesis-driven functional experiments are undertaken.

Statistical fine-mapping jointly considers correlated groups of associated variants to estimate the likely causality of each (45). This has been undertaken for several psoriasis susceptibility loci, revealing multiple independent association signals (46).

Pathway analysis methods look for known biological pathways for which gene annotations are enriched across multiple susceptibility loci. NF-κB and type I interferon signalling pathways have thus been implicated in psoriasis pathogenesis (36).

If GWAS summary results are available from other studies that have assessed the genetic basis of relevant molecular traits, colocalisation with the disease association signal can be assessed (47, 48). In particular, expression quantitative trait loci (eQTLs) are SNPs associated with the level of expression of a gene in a specific tissue. Colocalisation of a psoriasis susceptibility signal and a skin- or immune-based eQTL would thus provide strong evidence that the variant directly modifies psoriasis risk and suggest a probable mechanism of action. This powerful approach has been successfully employed in GWAS studies of acne (49) and atopic dermatitis (50) but has yet to be employed systematically in a large psoriasis dataset, with only suggestive colocalisations being reported in cross-disease studies (51, 52).

It is worth remarking that all of these approaches rely to a greater or lesser extent on *open science*: the continuing efforts of research groups around the world that are committed to making reference data, summary results, annotations, tools and computational resources publicly available in the interests of collaborative science.

TRANSLATION OF GENETIC DISCOVERIES INTO NOVEL THERAPEUTICS

The genetic insights gained from large-scale association analyses have paved the way for transformative novel therapeutics in psoriasis. Indeed, it has been shown in general that pipeline drugs whose mechanisms are supported by direct genetic evidence are more likely to reach the clinic (53, 54). Based on the mechanistic insights that have emerged from genetic studies in psoriasis, the IL-23/T17 axis has been a particular focus for drug development. Biologic agents such as ustekinumab (targeting the common p40 subunit of IL-12 and IL-23), secukinumab and ixekizumab (targeting IL-17A), and newer monoclonal antibodies targeting the p19 subunit specific to IL-23 (including guselkumab and tildrakizumab), have shown progressively increasing efficacy rates in clinical trials (55). These agents are now licensed for use in the USA and Europe and have impressive effectiveness and tolerability in real world practice (55, 56).

In addition to informing the targets of biologic medications, genetic studies have opened new avenues for small molecule therapeutics. Following genetic association data highlighting *TYK2* as a causal allele (31, 32), an oral, selective
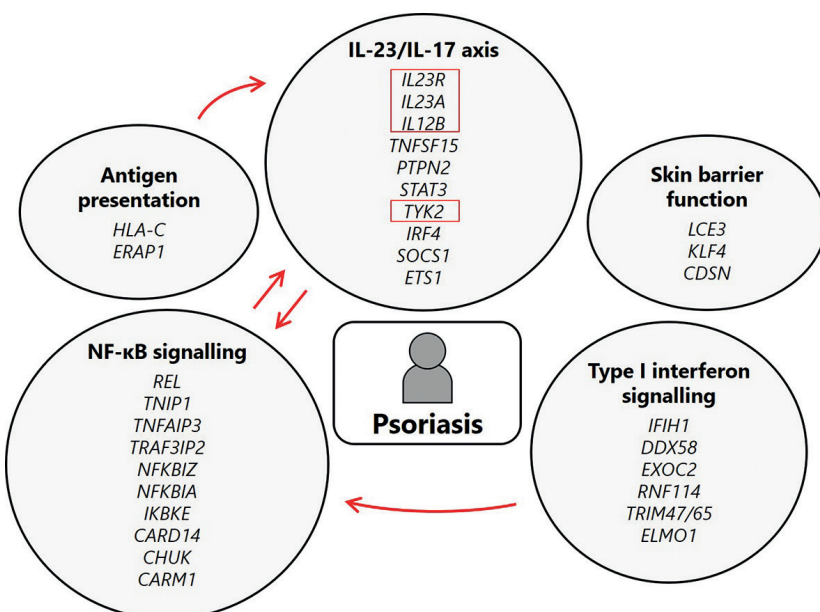
Fig. 1. Biological pathways implicated in psoriasis pathogenesis via genome wide association studies (GWAS). Candidate causal genes from selected disease-associated loci identified by GWAS. *Arrows* signify the crosstalk between the immune pathways shown (e.g. interleukin (IL)-17 and type I interferon signalling both activate nuclear factor-κB (NF-κB) pathways). *Red boxes*: genes involved in mechanisms currently targeted by psoriasis treatments.

inhibitor was developed, which has shown promising efficacy in phase II trials (57).

Missing heritability

Despite the recent progress in psoriasis genetics, less than a quarter of heritability is thought to be explained by the susceptibility loci identified to date (32). There are several reasons for this missing heritability.

A substantial fraction of heritability may arise from rare variants that are not genotyped or well tagged by GWAS arrays. A recent analysis of 22,000 whole genomes makes a compelling case for this, since the heritability of both height and body mass index could be almost fully explained when very rare variants are accounted for (suggesting also that pedigree-based estimates of heritability are not overestimated) (58). The same may be true for psoriasis susceptibility, although sequencing efforts will need to surpass those performed to date (59) to confirm this.

More generally, the estimated heritability explained at a GWAS-identified locus may be underestimated where the lead GWAS SNP is a poor tag for the true causal variant, or where there are multiple true causal variants (60).

Another explanation could be high polygenicity, where many common SNPs across the genome may modify psoriasis risk, but with effect sizes too small to have been identified with current GWAS sample sizes. Although increasingly large case-control study populations will help to address this (61), sufficient numbers to fully elucidate the role in psoriasis pathogenesis of every individual common SNP are impractical. One approach to overcoming this limitation is to consider genetic variation aggregated according to known biological function. For example, functional network-based analyses have been applied to suggest novel mechanisms involved in psoriasis (36, 62).

It could also be the case that psoriasis risk attributable to individual genetic variants does not accumulate additively and independently, so that simple GWAS association tests mask more complex causal biology. Alternative models of genetic architecture have been explored (63), including genetic interactions genome-wide (64, 65) (recall the *HLA-C/ERAP1* interaction described previously).

Missing heritability in genetic studies could be due in part to epigenetic variation: DNA modifications that can cause differences in gene expression even when no differences are present in DNA sequence. Numerous studies have begun to explore the role of epigenetics in psoriasis, although the types of modification and study designs have varied widely, making it difficult to assess their overall contribution to heritability (66).

The complex genetic nature of psoriasis and the unresolved missing heritability have implications for the growing industry of direct-to-consumer genetic testing. While genetic risk profiles can offer additional information beyond family-history based risk estimates (67), this information will likely be insufficiently precise or consistent to offer substantial clinical utility (68, 69) and it is vulnerable to misunderstanding by the public (70, 71).

As we shall describe, however, the genetic risk profiles of larger cohorts still hold great potential to refine our understanding of the biology and to inform effective clinical management of psoriasis.
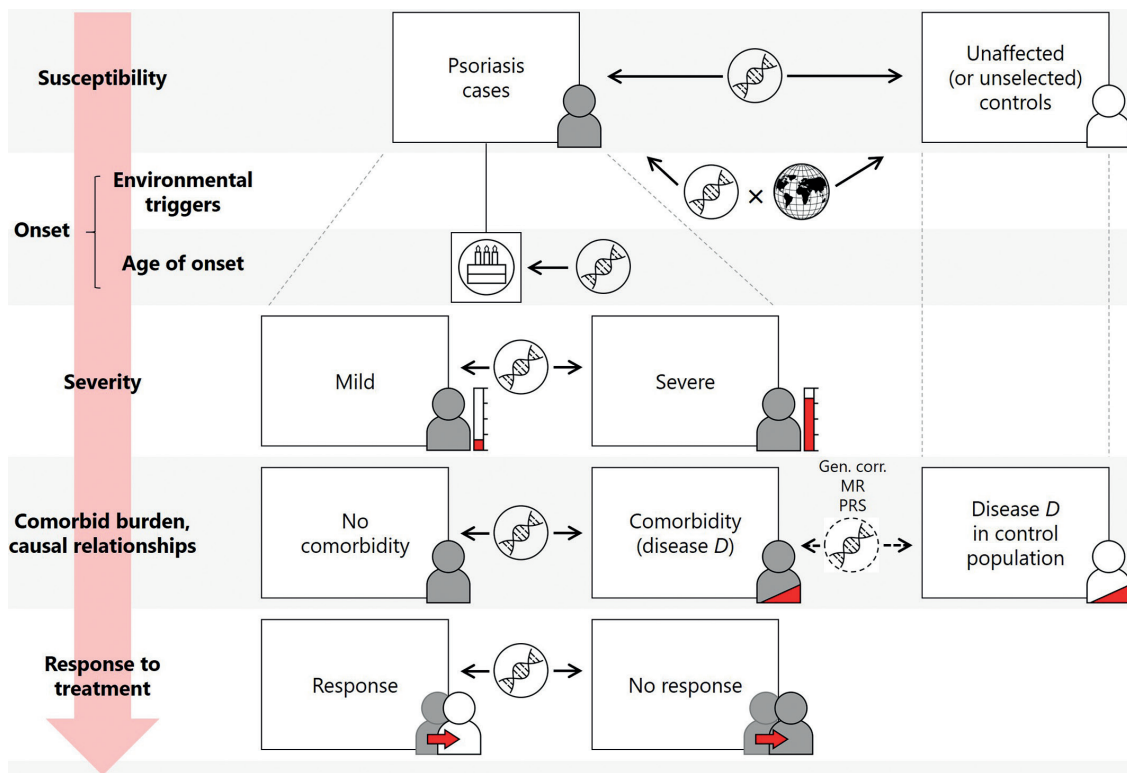
BEYOND DISEASE SUSCEPTIBILITY

The possibilities of GWAS-based analysis have now moved beyond the study of simple susceptibility and towards disease stratification. With large collections of genotyped and deeply phenotyped individuals, the genetic basis of many other aspects of psoriasis natural history and treatment response can be characterised (**Fig. 2**). These collections could comprise psoriasis patients (e.g. PSORT (72)) or be derived from the general population with phenotype data from linked electronic medical records (e.g. UK Biobank (73)).

These "post-susceptibility" genetic studies still currently utilise much smaller samples than the susceptibility GWAS meta-analyses described above. However, they can benefit from numerous methods that incorporate or compare genetic information (typically GWAS summary statistics) from related traits to make novel inferences. Relevant methods include polygenic risk scores (PRS) (74) and genetic correlation (75, 76) to assess shared genetic associations, Mendelian randomisation (77) to assess causality, and methods for deconvoluting genome-wide association signals into functionally relevant constituents (78) (Box 1). While findings from psoriasis susceptibility studies offer a natural starting point (and efforts to accurately document and annotate these associations are ongoing (79, 80)), the utility of these methods are greatly enhanced by the availability of GWAS summary results for thousands of other traits, including physiological, disease-based and molecular traits (81).

We offer here a brief overview of recent progress in psoriasis genetics beyond susceptibility.

Onset

It remains unclear how genetic susceptibility variants interact with environmental risk factors such as infection, ultraviolet exposure, smoking, alcohol, and psychological stress to trigger psoriasis onset (82). Initial findings suggest that the risk attributable to *HLA-C*06:02* may be modified by smoking and stress (83). The pathogenic contribution of smoking may also be mediated via variants in *CYP1A1*, a key gene in the aryl hydrocarbon receptor signalling pathway (84). The availability of large datasets with environmental exposure and GWAS

Fig. 2. Psoriasis genetics beyond susceptibility. Various strategies are employed to study the genetic factors that influence the conceptual trajectory from risk of psoriasis through disease onset and prognosis to patient outcomes (red arrow). *Susceptibility*: allele frequencies are compared between psoriasis cases and controls to reveal genetic variants contributing to psoriasis risk. *Onset:* gene × environment studies may integrate genetic data with environmental exposures (indicated by globe symbol) to identify relationships between genes and environmental triggers; age-of-onset is also influenced by genetic factors and this can be investigated where age-of-onset data (denoted by birthday cake symbol) are available for psoriasis cases. *Severity:* genetic profiles can be compared between psoriasis patients with mild and severe disease; severity may also be studied as a continuous outcome. *Comorbidities*: genetic profiles are compared between psoriasis patients with and without comorbid disease *D*; more sophisticated methods will also consider the genetic basis of disease *D* in the wider population. *Response to treatment*: genetic profiles can be compared between psoriasis patients responding and not responding to a treatment; response may also be studied as a continuous outcome. Gen. corr.: genetic correlation; MR: Mendelian randomisation; PRS: polygenic risk score.

data (such as UK Biobank (73)) now offers the opportunity to study gene-environment interactions in a more systematic manner, and this is an active area of research in the field. Age of onset is better studied. It is well established that the *HLA-C*06:02* susceptibility allele is associated with earlier disease onset (85, 86). Tsoi et al. used PRS analysis to show that a greater burden of psoriasis susceptibility variants is associated with earlier disease onset, even when only non-HLA susceptibility loci are considered (36).

Comorbidities

Psoriatic arthritis (PsA), with prevalence estimates ranging from 6–41% among individuals with psoriasis (87), has been the subject of large genetic studies as a disease in its own right (88–90). Particularly revealing, however, are studies comparing individuals with psoriasis and PsA against cutaneous-only psoriasis cases, (either directly or with reference to unaffected controls). Several studies focusing on the HLA region suggest that certain *HLA-B* alleles, including *HLA-B*27*, are associated with increased PsA risk in the presence of

psoriasis (21, 91, 92), while *HLA-C*06:02* is not (91). Genome-wide analysis has identified additional associations of interest, including independent alleles in known psoriasis susceptibility loci (including at *IL23R* and *TNFAIP3*) (93). The translational potential of these approaches was recently explored using a "risk score" of 200 genetic markers that proved predictive of PsA development (area under the receiver operator curve = 0.82) (37). While this finding requires replication and may benefit from phenotype refinement (there are at least five recognised subtypes of PsA (94)), it offers a first step towards prognostic genetic risk profiling.

Obesity and related cardiometabolic traits have also been studied. While a large GWAS-based investigation found the genetic architectures of psoriasis and cardiometabolic traits to be largely distinct (95), an epidemiological association with obesity is well established (96, 97) and twin studies suggest a genetic correlation (98). Based on psoriasis and body mass index (BMI) GWAS data, Mendelian randomisation reveals a causal relationship: higher BMI increases the risk of psoriasis, whereas psoriasis does not have a causal effect on BMI (99, 100). Given the relatively large effect that *HLA-C*06:02* exerts

on psoriasis risk, it may be interesting to examine the causal role of BMI separately in patients positive and negative for this allele.

In principle, the shared genetic aetiology between psoriasis and any other associated condition can be readily explored at scale via GWAS data. A recent example looked at psoriasis alongside 4 other inflammatory diseases (ankylosing spondylitis, Crohn's disease, primary sclerosing cholangitis and ulcerative colitis), finding genetic overlap between the conditions that may drive co-occurrence, but with the qualification that patients affected by multiple conditions are likely to be genetically distinct from those with a single disease (101). Shared genetic factors have been found to extend beyond inflammatory disease, such as the positive genetic correlation observed between psoriasis and schizophrenia (102).

Stratified medicine

Genomic information has an exciting role in potential future personalised models of disease prevention and treatment (103). Although highly discriminative genetic prediction for complex diseases such as psoriasis (which are influenced by many genetic factors of modest effect) is unlikely (74), there remains ample opportunity to "stratify" individuals into broader groups according to distinct risk and response profiles, thus leading to more effective and economical care.

Effective deployment of expensive biologic therapies is an area of promise in psoriasis. Patients positive for the *HLA-C*06:02* psoriasis susceptibility allele demonstrate better response to ustekinumab than *HLA-C*06:02*-negative patients, particularly during the initial months of treatment (104, 105). Numerous candidate gene studies (and one small GWAS (106)), have tested for genetic associations with response to TNF antagonists such as etanercept, adalimumab and infliximab, often pooling observations for multiple drugs. Robust associations have until recently been scarce, but we are beginning to see better-powered investigations; a recent Danish study found significant associations with anti-TNF response in several immune genes (107). We recently showed via a comparative approach that *HLA-C*06:02* status could inform choice of treatment between adalimumab and ustekinumab, particularly when used in combination with clinical factors. Specifically, we found that *HLA-C*06:02*-negative patients with psoriatic arthritis were significantly more likely to respond to adalimumab than ustekinumab after 6 months (odds ratio, 5.98; $p = 6.89 \times 10^{-5}$), with no such difference observed in *HLA-C*06:02*-positive patients (108). This has promising clinical utility.

PRS may also help to define strata relevant to the management of psoriasis. Several studies have explored the predictive ability of PRS in psoriasis susceptibility (36, 109, 110) but the true translational benefits of this approach may lie in identifying and characterising groups of patients with very high or very low PRS scores (74). More research in this area in psoriasis is therefore warranted.

PUSTULAR PSORIASIS

Pustular psoriasis is a rare subtype characterised clinically by the presence of sterile pustules on variably erythematous skin, and histologically by diffuse dermal neutrophilic infiltration (111). It can be classified as either acute generalised (generalised pustular psoriasis (GPP)) or chronic localised disease (palmoplantar pustulosis (PPP) and acrodermatitis continua of Hallopeau (ACH)) (112). Pustular psoriasis has a distinct genetic architecture to plaque psoriasis, underscored by a lack of association with the *PSORS1* locus (113). The severity and rarity of the clinical phenotype indicate that pustular psoriasis could be associated with rare alleles of moderate to large effect, which has been supported by the identification of three disease genes (*IL36RN, AP1S3* and *CARD14*) using next-generation sequencing technologies (Box 1).

Linkage studies of consanguineous pedigrees and exome sequencing of unrelated GPP patients identified autosomal recessive loss of function mutations in *IL36RN* (114, 115). *IL36RN* encodes the IL-36 receptor antagonist (IL-36Ra), which modulates the activity of the IL-1 family cytokines IL-36α, -β and -γ. The screening of expanded patient resources subsequently identified a spectrum of *IL36RN* mutations that are distributed throughout the length of the protein and are associated with pustular psoriasis in a variety of populations (116, 117).

Genotype-phenotype analyses indicate that *IL36RN* disease alleles are less common in individuals with PPP (frequency 0.03) than GPP (0.19) and ACH (0.16) (116). Although recessive *IL36RN* alleles are typically observed in patients presenting with a severe clinical phenotype (early-onset GPP characterised by a high risk of systemic involvement) (118), deleterious *IL36RN* variants have also been associated with localised pustular disease (119). Individuals harbouring a single *IL36RN* mutation are occasionally affected, and they classically present with disease at a later age, indicating a dose-dependent effect (116, 118). Thus, genotype-phenotype analyses provide evidence for variable penetrance of disease alleles and a potential role for genetic modifiers and environmental factors.

Since *IL36RN* mutations are only found in a minority (~25%) of pustular psoriasis cases (118), exome sequencing was undertaken to gain a better understanding of the genetic basis of the disease. This uncovered two recurring founder mutations in the *AP1S3* gene (120). While these defects were found to account for 12% of pustular psoriasis cases of European descent, no AP1S3 mutations were found in Asian patients. AP1S3 encodes the σ1 subunit of AP-1, an evolutionarily conserved

hetero-tetramer that has been implicated in the formation of autophagosomes (specialised vesicles that mediate autophagy). Autophagy is an intracellular degradation pathway for misfolded proteins and damaged organelles (121) and has been shown to regulate cutaneous immune responses (122, 123). *AP1S3* mutations may lead to defective autophagy, causing accumulation of p62 (an adaptor protein that mediates NF-kB activation) and upregulation of IL-36 mediated cutaneous inflammation (124). Therefore, mutations in different disease genes converge on the de-regulation of IL-36 signalling in pustular psoriasis, highlighting IL-36 blockade as a promising therapeutic strategy regardless of the specific gene affected.

CARD14 was subsequently confirmed as a third disease gene for GPP (25). *CARD14* is highly expressed in keratinocytes and encodes a scaffold protein that, upon oligomerisation, mediates TRAF-2 dependent activation of NF-κB signalling. A deleterious gain-of-function substitution in *CARD14* has been associated with GPP in an extended case series and shown to cause spontaneous CARD14 oligomerisation *in vitro* (25). The same variant was also found in two patients with PPP (125), which provides further evidence for an overlap in the genetic basis of generalised and localised forms of pustular psoriasis. Indeed, gain-of-function *CARD14* mutations have been detected in cases of familial plaque psoriasis (23, 24), indicating shared aetiological mechanisms in plaque and pustular subtypes of disease.

There is a substantial unmet need for effective treatments for pustular psoriasis (111). The conventional systemic agents used for the treatment of plaque psoriasis are often ineffective in pustular phenotypes and there is a paucity of robust clinical trial data, such that current guidelines are mostly based on isolated case reports (111). However, recent exciting progress in this area shows a clear throughline from genetic discovery to treatment advances. IL-1 blockers are being investigated as potential treatments for pustular psoriasis and a multi-centre double-blind randomised controlled trial of ana-kinra in PPP is currently underway (http://apricot-trial.com/). In GPP, anakinra has been shown to cause initial rapid clinical improvements in case reports (126, 127), although full disease remission was seldom achieved. This incomplete response supports the notion that IL-1 itself is not the dominant disease driver but participates in positive regulatory feedback loops driven by IL-36 (128).

In vivo and *ex vivo* research has validated IL-36 signalling as a powerful therapeutic target in psoriasis, and indicates that IL-36 blockade would not substantially compromise host defences (129). A recent phase I proof of concept study of 7 patients demonstrated that blockade of the IL-36 receptor (using a single intravenous dose of a monoclonal antibody) reduced the severity of GPP over a 20-week period (130). The agent was efficacious irrespective of the presence of known causal genetic va-

riants and larger scale clinical trials of IL-36 antagonists in pustular psoriasis are currently underway.

FINAL THOUGHTS

Non-European ethnicities

We have shown that genetics will be instrumental in moving healthcare provision towards stratified, and even personalised, models. However, such progress is dependent on robust genetic associations with disease susceptibility, clinical outcomes and other related traits. The majority of genotyping efforts to date have focused on populations of European, and to a lesser extent Han Chinese, origin, meaning the translational potential of GWAS is largely limited to these groups at present.

A trans-ethnic GWAS meta-analysis of psoriasis susceptibility demonstrated heterogeneous genetic associations between European and Han Chinese populations (20). Other ethnic groups in which smaller GWAS and candidate gene studies have been undertaken include Indian (131), Japanese (132) and Omani Arab (133) populations. We are unaware of genetic studies of psoriasis in people of African descent. While lower prevalence might make psoriasis a smaller population burden among predominantly non-white populations (134) the disease burden for individual psoriasis patients is high, and large-scale genetic studies across ethnic groups are warranted.

Such endeavours will benefit from recent community efforts to generate the necessary supporting resources, including statistical tools for trans-ethnic meta-analysis (135), reference panels for genome-wide (136) and HLA allele (137) imputation, and GWAS summary results for common traits (138).

The future of genetics in psoriasis

As with other complex diseases, we believe that genetics will be at the heart of future success in translational psoriasis research. Increasingly large GWAS studies will improve power to detect genetic variants with small effects on psoriasis risk, refining our understanding of the genetic basis of the disease. This increased resolution should allow more accurate deconvolution of susceptibility associations into functional mechanisms of disease, aided by a growing catalogue of systematically derived and publicly available GWAS datasets for intermediate molecular traits. There is also an increasing awareness in the investigative dermatology community of the importance of precise phenotyping. When combined with genetic data, larger and more detailed clinical datasets will help reveal genetic differences between patients that differ in phenotypic presentation or outcome and therefore inform the development and deployment of effective therapies. Finally, as patients become more likely to undergo GWAS profiling or whole-genome sequencing as part of standard healthcare provision, there will almost

certainly be benefits to be derived from PRS or related genome-wide measures. These benefits are unlikely to come from very precise diagnostic or prognostic predictions but rather from prioritising individuals for early screening or closer monitoring, thus making optimal use of clinical resources and reducing the significant disease burden of psoriasis at the population level.

ACKNOWLEDGMENTS

REFERENCES

1. Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, et al. Initial sequencing and analysis of the human genome. Nature 2001; 409: 860–921.
2. Venter JC, Adams MD, Myers EW, Li PW, Mural RJ, Sutton GG, et al. The sequence of the human genome. Science 2001; 291: 1304–1351.
3. Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med 2009; 361: 496–509.
4. World Health Organisation. Global Report on Psoriasis. World Health Organisation (http://www.who.int/iris/handle/10665/204417), 2016.
5. Elder JT, Nair RP, Guo SW, Henseler T, Christophers E, Voorhees JJ. The genetics of psoriasis. Arch Dermatol 1994; 130: 216–224.
6. Lomholt G. Psoriasis: prevalence, spontaneous course, and genetics. A Census Study on the prevalaence of skin diseases on the Faroe Islands: GEC Gad; 1963.
7. Andressen C, Henseler T. Die Erblichkeit der Psoriasis: Eine Analyse von 2,035 Familienanarnnesen. Hautarzt 1982; 33: 214–217.
8. Brandrup F, Hauge M, Henningsen K, Eriksen B. Psoriasis in an Unselected Series of Twins. JAMA Dermatology 1978; 114: 874–878.
9. Duffy DL, Spelman LS, Martin NG. Psoriasis in Australian twins. J Am Acad Dermatol 1993; 29: 428–434.
10. Farber EM, Nall ML, Watson W. Natural History of Psoriasis in 61 Twin Pairs. JAMA Dermatology 1974; 109: 207–211.
11. Capon F, Trembath RC, Barker JN. An update on the genetics of psoriasis. Dermatol Clin 2004; 22: 339–347, vii.
12. Trembath RC, Clough RL, Rosbotham JL, Jones AB, Camp RD, Frodsham A, et al. Identification of a major susceptibility locus on chromosome 6p and evidence for further disease loci revealed by a two stage genome-wide search in psoriasis. Hum Mol Genet 1997; 6: 813–820.
13. Nair RP, Henseler T, Jenisch S, Stuart P, Bichakjian CK, Lenk W, et al. Evidence for two psoriasis susceptibility loci (HLA and 17q) and two novel candidate regions (16q and 20p) by genome-wide scan. Hum Mol Genet 1997; 6: 1349–1356.
14. Veal CD, Capon F, Allen MH, Heath EK, Evans JC, Jones A, et al. Family-based analysis using a dense single-nucleotide polymorphism-based map defines genetic variation at PSORS1, the major psoriasis-susceptibility locus. Am J Hum Genet 2002; 71: 554–564.
15. Jonca N, Leclerc EA, Caubet C, Simon M, Guerrin M, Serre G. Corneodesmosomes and corneodesmosin: from
16. the stratum corneum cohesion to the pathophysiology of genodermatoses. Eur J Dermatol 2011; 21 Suppl 2: 35–42.
16. Alper CA, Larsen CE, Dubey DP, Awdeh ZL, Fici DA, Yunis EJ. The haplotype structure of the human major histocompatibility complex. Hum Immunol 2006; 67: 73–84.
17. Nair RP, Duffin KC, Helms C, Ding J, Stuart PE, Goldgar D, et al. Genome-wide scan reveals association of psoriasis with IL-23 and NF-kappaB pathways. Nat Genet 2009; 41: 199–204.
18. Strange A, Capon F, Spencer CC, Knight J, Weale ME, Allen MH, et al. A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. Nat Genet 2010; 42: 985–990.
19. Feng BJ, Sun LD, Soltani-Arabshahi R, Bowcock AM, Nair RP, Stuart P, et al. Multiple Loci within the major histocompatibility complex confer risk of psoriasis. PLOS Genet 2009; 5: e1000606.
20. Yin X, Low HQ, Wang L, Li Y, Ellinghaus E, Han J, et al. Genome-wide meta-analysis identifies multiple novel associations and ethnic heterogeneity of psoriasis susceptibility. Nat Commun 2015; 6: 6916.
21. Okada Y, Han B, Tsoi LC, Stuart PE, Ellinghaus E, Tejasvi T, et al. Fine mapping major histocompatibility complex associations in psoriasis and its clinical subtypes. Am J Hum Genet 2014; 95: 162–172.
22. Knight J, Spain SL, Capon F, Hayday A, Nestle FO, Clop A, et al. Conditional analysis identifies three novel major histocompatibility complex loci associated with psoriasis. Hum Mol Genet 2012; 21: 5185–5192.
23. Jordan CT, Cao L, Roberson ED, Duan S, Helms CA, Nair RP, et al. Rare and common variants in CARD14, encoding an epidermal regulator of NF-kappaB, in psoriasis. Am J Hum Genet 2012; 90: 796–808.
24. Jordan CT, Cao L, Roberson ED, Pierson KC, Yang CF, Joyce CE, et al. PSORS2 is due to mutations in CARD14. Am J Hum Genet 2012; 90: 784–795.
25. Berki DM, Liu L, Choon SE, David Burden A, Griffiths CEM, Navarini AA, et al. Activating CARD14 Mutations Are Associated with Generalized Pustular Psoriasis but Rarely Account for Familial Recurrence in Psoriasis Vulgaris. J Invest Dermatol 2015; 135: 2964–2970.
26. de Cid R, Riviera-Munoz E, Zeeuwen PL, Robarge J, Liao W, Dannhauser EN, et al. Deletion of the late cornified envelope LCE3B and LCE3C genes as a susceptibility factor for psoriasis. Nat Genet 2009; 41: 211–215.
27. Zhang XJ, Huang W, Yang S, Sun LD, Zhang FY, Zhu QX, et al. Psoriasis genome-wide association study identifies susceptibility variants within LCE gene cluster at 1q21. Nat Genet 2009; 41: 205–210.
28. Ellinghaus E, Ellinghaus D, Stuart PE, Nair RP, Debrus S, Raelson JV, et al. Genome-wide association study identifies a psoriasis susceptibility locus at TRAF3IP2. Nat Genet 2010; 42: 991–995.
29. Stuart PE, Nair RP, Ellinghaus E, Ding J, Tejasvi T, Gudjonsson JE, et al. Genome-wide association analysis identifies three psoriasis susceptibility loci. Nat Genet 2010; 42: 1000–1004.
30. Cortes A, Brown MA. Promise and pitfalls of the Immunochip. Arthritis Res Ther 2011; 13: 101.
31. Tsoi LC, Spain SL, Knight J, Ellinghaus E, Stuart PE, Capon F, et al. Identification of 15 new psoriasis susceptibility loci highlights the role of innate immunity. Nat Genet 2012; 44: 1341–1348.
32. Dand N, Mucha S, Tsoi LC, Mahil SK, Stuart PE, Arnold A, et al. Exome-wide association study reveals novel psoriasis susceptibility locus at TNFSF15 and rare protective alleles in genes contributing to type I IFN signalling. Hum Mol Genet 2017; 26: 4301–4313.
33. Das S, Forer L, Schonherr S, Sidore C, Locke AE, Kwong A, et al. Next-generation genotype imputation service and methods. Nat Genet 2016; 48: 1284–1287.
34. McCarthy S, Das S, Kretzschmar W, Delaneau O, Wood AR, Teumer A, et al. A reference panel of 64,976 haplotypes for genotype imputation. Nat Genet 2016; 48: 1279–1283.

35. Tsoi LC, Elder JT, Abecasis GR. Graphical algorithm for integration of genetic and biological data: proof of principle using psoriasis as a model. Bioinformatics 2015; 31: 1243–1249.

36. Tsoi LC, Stuart PE, Tian C, Gudjonsson JE, Das S, Zawistowski M, et al. Large scale meta-analysis characterizes genetic architecture for common psoriasis associated variants. Nat Commun 2017; 8: 15382.

37. Patrick MT, Stuart PE, Raja K, Gudjonsson JE, Tejasvi T, Yang J, et al. Genetic signature to provide robust risk assessment of psoriatic arthritis development in psoriasis patients. Nat Commun 2018; 9: 4178.

38. Tsoi LC, Spain SL, Ellinghaus E, Stuart PE, Capon F, Knight J, et al. Enhanced meta-analysis and replication studies identify five new psoriasis susceptibility loci. Nat Commun 2015; 6: 7001.

39. Zuo X, Sun L, Yin X, Gao J, Sheng Y, Xu J, et al. Whole-exome SNP array identifies 15 new susceptibility loci for psoriasis. Nat Commun 2015; 6: 6793.

40. Capon F, Bijlmakers MJ, Wolf N, Quaranta M, Huffmeier U, Allen M, et al. Identification of ZNF313/RNF114 as a novel psoriasis susceptibility gene. Hum Mol Genet 2008; 17: 1938–1945.

41. Cargill M, Schrodi SJ, Chang M, Garcia VE, Brandon R, Callis KP, et al. A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes. Am J Hum Genet 2007; 80: 273–290.

42. Stuart PE, Huffmeier U, Nair RP, Palla R, Tejasvi T, Schalkwijk J, et al. Association of beta-defensin copy number and psoriasis in three cohorts of European origin. J Invest Dermatol 2012; 132: 2407–2413.

43. Pappu BP, Borodovsky A, Zheng TS, Yang X, Wu P, Dong X, et al. TL1A-DR3 interaction regulates Th17 cell function and Th17-mediated autoimmune disease. J Exp Med 2008; 205: 1049–1062.

44. Mahil SK, Capon F, Barker JN. Update on psoriasis immunopathogenesis and targeted immunotherapy. Semin Immunopathol 2016; 38: 11–27.

45. Spain SL, Barrett JC. Strategies for fine-mapping complex traits. Hum Mol Genet 2015; 24: R111–119.

46. Das S, Stuart PE, Ding J, Tejasvi T, Li Y, Tsoi LC, et al. Fine mapping of eight psoriasis susceptibility loci. Eur J Hum Genet 2015; 23: 844–853.

47. Hormozdiari F, van de Bunt M, Segrè Ayellet V, Li X, Joo Jong Wha J, Bilow M, et al. Colocalization of GWAS and eQTL signals detects target genes. Am J Hum Genet 2016; 99: 1245–1260.

48. Giambartolomei C, Vukcevic D, Schadt EE, Franke L, Hingorani AD, Wallace C, et al. Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. PLoS Genet 2014; 10: e1004383.

49. Petridis C, Navarini AA, Dand N, Saklatvala J, Baudry D, Duckworth M, et al. Genome-wide meta-analysis implicates mediators of hair follicle development and morphogenesis in risk for severe acne. Nat Commun 2018; 9: 5075.

50. Paternoster L, Standl M, Waage J, Baurecht H, Hotze M, Strachan DP, et al. Multi-ancestry genome-wide association study of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis. Nat Genet 2015; 47: 1449–1456.

51. Raj T, Rothamel K, Mostafavi S, Ye C, Lee MN, Replogle JM, et al. Polarization of the effects of autoimmune and neurodegenerative risk alleles in leukocytes. Science 2014; 344: 519–523.

52. Guo H, Fortune MD, Burren OS, Schofield E, Todd JA, Wallace C. Integration of disease association and eQTL data using a Bayesian colocalisation approach highlights six candidate causal genes in immune-mediated diseases. Hum Mol Genet 2015; 24: 3305–3313.

53. Nelson MR, Tipney H, Painter JL, Shen J, Nicoletti P, Shen Y, et al. The support of human genetic evidence for approved drug indications. Nat Genet 2015; 47: 856.

54. Cook D, Brown D, Alexander R, March R, Morgan P, Satterthwaite G, et al. Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework. Nat Rev Drug Discov 2014; 13: 419.

55. Menter A, Strober BE, Kaplan DH, Kivelevitch D, Prater EF, Stoff B, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. J Am Acad Dermatol 2019; 80: 1029–1072.

56. National Institute for Health and Care Excellence. Psoriasis: assessment and management. NICE guideline (CG153). 2012; updated September 2017.

57. Papp K, Gordon K, Thaci D, Morita A, Gooderham M, Foley P, et al. Phase 2 Trial of selective tyrosine kinase 2 inhibition in psoriasis. N Engl J Med 2018; 379: 1313–1321.

58. Wainschtein P, Jain DP, Yengo L, Zheng Z, Cupples LA, Shadyab AH, et al. Recovery of trait heritability from whole genome sequence data. bioRxiv 2019: 588020.

59. Tang H, Jin X, Li Y, Jiang H, Tang X, Yang X, et al. A large-scale screen for coding variants predisposing to psoriasis. Nat Genet 2014; 46: 45–50.

60. Gusev A, Bhatia G, Zaitlen N, Vilhjalmsson BJ, Diogo D, Stahl EA, et al. Quantifying missing heritability at known GWAS loci. PLoS Genet 2013; 9: e1003993.

61. Wood AR, Esko T, Yang J, Vedantam S, Pers TH, Gustafsson S, et al. Defining the role of common variation in the genomic and biological architecture of adult human height. Nat Genet 2014; 46: 1173–1186.

62. Aterido A, Julia A, Ferrandiz C, Puig L, Fonseca E, Fernandez–Lopez E, et al. Genome-wide pathway analysis identifies genetic pathways associated with psoriasis. J Invest Dermatol 2016; 136: 593–602.

63. Wei WH, Massey J, Worthington J, Barton A, Warren RB. Genotypic variability-based genome-wide association study identifies non-additive loci HLA-C and IL12B for psoriasis. J Hum Genet 2018; 63: 289–296.

64. Lee KY, Leung KS, Tang NLS, Wong MH. Discovering genetic factors for psoriasis through exhaustively searching for significant second order SNP-SNP interactions. Sci Rep 2018; 8: 15186.

65. Dou J, Guo H, Cheng F, Huang H, Fu L, Li L, et al. Genotype combination contributes to psoriasis: An exhaustive algorithm perspective. PLoS One 2017; 12: e0186067.

66. Pollock RA, Abji F, Gladman DD. Epigenetics of psoriatic disease: A systematic review and critical appraisal. J Autoimmun 2017; 78: 29–38.

67. Aiyar L, Shuman C, Hayeems R, Dupuis A, Pu S, Wodak S, et al. Risk estimates for complex disorders: comparing personal genome testing and family history. Genet Med 2014; 16: 231–237.

68. Kalf RR, Mihaescu R, Kundu S, de Knijff P, Green RC, Janssens AC. Variations in predicted risks in personal genome testing for common complex diseases. Genet Med 2014; 16: 85–91.

69. Statement of the ESHG on direct-to-consumer genetic testing for health-related purposes. Eur J Hum Genet 2010; 18: 1271–1273.

70. Nordgren A. Neither as harmful as feared by critics nor as empowering as promised by providers: risk information offered direct to consumer by personal genomics companies. J Community Genet 2014; 5: 59–68.

71. Leighton JW, Valverde K, Bernhardt BA. The general public's understanding and perception of direct–to-consumer genetic test results. Public Health Genomics 2012; 15: 11–21.

72. Griffiths CEM, Barnes MR, Burden AD, Nestle FO, Reynolds NJ, Smith CH, et al. Establishing an Academic-Industrial Stratified Medicine Consortium: psoriasis stratification to optimize relevant therapy. J Invest Dermatol 2015; 135: 2903–2907.

73. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, et al. The UK Biobank resource with deep phenotyping and genomic data. Nature 2018; 562: 203–209.

74. Lewis CM, Vassos E. Prospects for using risk scores in polygenic medicine. Genome Med 2017; 9: 96.

75. Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh PR, et al. An atlas of genetic correlations across human diseases and traits. Nat Genet 2015; 47: 1236–1241.

76. Lee SH, Yang J, Goddard ME, Visscher PM, Wray NR. Estimation of pleiotropy between complex diseases using single-nucleotide polymorphism-derived genomic relationships and restricted maximum likelihood. Bioinformatics 2012; 28: 2540–2542.

77. Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. Hum Mol Genet 2014; 23: R89–98.

78. Udler MS, Kim J, von Grotthuss M, Bonàs-Guarch S, Cole JB, Chiou J, et al. Type 2 diabetes genetic loci informed by multi-trait associations point to disease mechanisms and subtypes: A soft clustering analysis. PLoS Med 2018; 15: e1002654.

79. Aggarwal S, Nayek A, Pradhan D, Verma R, Yadav M, Ponnusamy K, et al. dbGAPs: A comprehensive database of genes and genetic markers associated with psoriasis and its subtypes. Genomics 2017 Oct 12. [Epub ahead of print].

80. Lin Y, Liu L, Sheng Y, Shen C, Zheng X, Zhou F, et al. A catalog of potential putative functional variants in psoriasis genome-wide association regions. PLoS One 2018; 13: e0196635.

81. Watanabe K, Stringer S, Frei O, Mirkov MU, Polderman TJC, van der Sluis S, et al. A global overview of pleiotropy and genetic architecture in complex traits. bioRxiv 2018: 500090.

82. Zeng J, Luo S, Huang Y, Lu Q. Critical role of environmental factors in the pathogenesis of psoriasis. J Dermatol 2017; 44: 863–872.

83. Jin Y, Yang S, Zhang F, Kong Y, Xiao F, Hou Y, et al. Combined effects of HLA-Cw6 and cigarette smoking in psoriasis vulgaris: a hospital-based case-control study in China. J Eur Acad Dermatol Venereol 2009; 23: 132–137.

84. Kramer U, Esser C. Cigarette smoking, metabolic gene polymorphism, and psoriasis. J Invest Dermatol 2006; 126: 693–694; author reply 695.

85. Henseler T, Christophers E. Psoriasis of early and late onset: characterization of two types of psoriasis vulgaris. J Am Acad Dermatol 1985; 13: 450–456.

86. Gudjonsson JE, Karason A, Runarsdottir EH, Antonsdottir AA, Hauksson VB, Jonsson HH, et al. Distinct clinical differences between HLA-Cw*0602 positive and negative psoriasis patients – an analysis of 1019 HLA-C- and HLA-B-typed patients. J Invest Dermatol 2006; 126: 740–745.

87. Ogdie A, Weiss P. The epidemiology of psoriatic arthritis. Rheum Dis Clin North Am 2015; 41: 545–568.

88. Bowes J, Budu-Aggrey A, Huffmeier U, Uebe S, Steel K, Hebert HL, et al. Dense genotyping of immune-related susceptibility loci reveals new insights into the genetics of psoriatic arthritis. Nat Commun 2015; 6: 6046.

89. Ellinghaus E, Stuart PE, Ellinghaus D, Nair RP, Debrus S, Raelson JV, et al. Genome-wide meta-analysis of psoriatic arthritis identifies susceptibility locus at REL. J Invest Dermatol 2012; 132: 1133–1140.

90. Aterido A, Canete JD, Tornero J, Ferrandiz C, Pinto JA, Gratacos J, et al. Genetic variation at the glycosaminoglycan metabolism pathway contributes to the risk of psoriatic arthritis but not psoriasis. Ann Rheum Dis 2019; 78. pii: e214158.

91. Bowes J, Ashcroft J, Dand N, Jalali-Najafabadi F, Bellou E, Ho P, et al. Cross-phenotype association mapping of the MHC identifies genetic variants that differentiate psoriatic arthritis from psoriasis. Ann Rheum Dis 2017; 76: 1774–1779.

92. Eder L, Chandran V, Pellett F, Shanmugarajah S, Rosen CF, Bull SB, et al. Differential human leucocyte allele association between psoriasis and psoriatic arthritis: a family-based association study. Ann Rheum Dis 2012; 71: 1361–1365.

93. Stuart PE, Nair RP, Tsoi LC, Tejasvi T, Das S, Kang HM, et al. Genome-wide association analysis of psoriatic arthritis and cutaneous psoriasis reveals differences in their genetic architecture. Am J Hum Genet 2015; 97: 816–836.

94. Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum 1973; 3: 55–78.

95. Koch M, Baurecht H, Ried JS, Rodriguez E, Schlesinger S, Volks N, et al. Psoriasis and cardiometabolic traits: modest association but distinct genetic architectures. J Invest Dermatol 2015; 135: 1283–1293.

96. Herron MD, Hinckley M, Hoffman MS, Papenfuss J, Hansen CB, Callis KP, et al. Impact of obesity and smoking on psoriasis presentation and management. Arch Dermatol 2005; 141: 1527–1534.

97. Cohen AD, Sherf M, Vidavsky L, Vardy DA, Shapiro J, Meyerovitch J. Association between psoriasis and the metabolic syndrome. A cross-sectional study. Dermatology 2008; 216: 152–155.

98. Lonnberg AS, Skov L, Skytthe A, Kyvik KO, Pedersen OB, Thomsen SF. Association of Psoriasis With the Risk for Type 2 Diabetes Mellitus and Obesity. JAMA Dermatol 2016; 152: 761–767.

99. Budu-Aggrey A, Brumpton B, Tyrrell J, Watkins S, Modalsli EH, Celis-Morales C, et al. Evidence of a causal relationship between body mass index and psoriasis: A mendelian randomization study. PLoS Med 2019; 16: e1002739.

100. Ogawa K, Stuart PE, Tsoi LC, Suzuki K, Nair RP, Mochizuki H, et al. A transethnic mendelian randomization study identifies causality of obesity on risk of psoriasis. J Invest Dermatol 2019; 139: 1397–1400.

101. Ellinghaus D, Jostins L, Spain SL, Cortes A, Bethune J, Han B, et al. Analysis of five chronic inflammatory diseases identifies 27 new associations and highlights disease-specific patterns at shared loci. Nat Genet 2016; 48: 510–518.

102. Pouget JG, Han B, Wu Y, Mignot E, Ollila HM, Barker J, et al. Cross-disorder analysis of schizophrenia and 19 immune-mediated diseases identifies shared genetic risk. Hum Mol Genet 2019 Jun 18. [Epub ahead of print].

103. Topol EJ. Individualized medicine from prewomb to tomb. Cell 2014; 157: 241–253.

104. Li K, Huang CC, Randazzo B, Li S, Szapary P, Curran M, et al. HLA-C*06:02 Allele and Response to IL-12/23 Inhibition: Results from the Ustekinumab Phase 3 Psoriasis Program. J Invest Dermatol 2016; 136: 2364–2371.

105. van Vugt LJ, van den Reek J, Coenen MJH, de Jong E. A systematic review of pharmacogenetic studies on the response to biologics in patients with psoriasis. Br J Dermatol 2018; 178: 86–94.

106. Nishikawa R, Nagai H, Bito T, Ikeda T, Horikawa T, Adachi A, et al. Genetic prediction of the effectiveness of biologics for psoriasis treatment. J Dermatol 2016; 43: 1273–1277.

107. Loft ND, Skov L, Iversen L, Gniadecki R, Dam TN, Brandslund I, et al. Associations between functional polymorphisms and response to biological treatment in Danish patients with psoriasis. Pharmacogenomics J 2018; 18: 494–500.

108. Dand N, Duckworth M, Baudry D, Russell A, Curtis CJ, Lee SH, et al. HLA-C*06:02 genotype is a predictive biomarker of biologic treatment response in psoriasis. J Allergy Clin Immunol 2019; 143: 2120–2130.

109. Kisiel B, Kisiel K, Szymanski K, Mackiewicz W, Bialo-Wojcicka E, Uczniak S, et al. The association between 38 previously reported polymorphisms and psoriasis in a Polish population: High predicative accuracy of a genetic risk score combining 16 loci. PLoS One 2017; 12: e0179348.

110. Stawczyk-Macieja M, Rebala K, Szczerkowska-Dobosz A, Wysocka J, Cybulska L, Kapinska E, et al. Evaluation of psoriasis genetic risk based on five susceptibility markers in a population from Northern Poland. PLoS One 2016; 11: e0163185.

111. Robinson A, Van Voorhees AS, Hsu S, Korman NJ, Lebwohl MG, Bebo BF, Jr., et al. Treatment of pustular psoriasis: from the Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol 2012; 67: 279–288.

112. Naik HB, Cowen EW. Autoinflammatory pustular neutrophilic diseases. Dermatol Clin 2013; 31: 405–425.

113. Asumalahti K, Ameen M, Suomela S, Hagforsen E, Michaelsson G, Evans J, et al. Genetic analysis of PSORS1 distinguishes guttate psoriasis and palmoplantar pustulosis. J Invest Dermatol 2003; 120: 627–632.

114. Onoufriadis A, Simpson MA, Pink AE, Di Meglio P, Smith CH, Pullabhatla V, et al. Mutations in IL36RN/IL1F5 are as-

sociated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. Am J Hum Genet 2011; 89: 432–437.

115. Marrakchi S, Guigue P, Renshaw BR, Puel A, Pei XY, Fraitag S, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. N Engl J Med 2011; 365: 620–628.

116. Twelves S, Mostafa A, Dand N, Burri E, Farkas K, Wilson R, et al. Clinical and genetic differences between pustular psoriasis subtypes. J Allergy Clin Immunol 2019; 143: 1021–1026.

117. Tauber M, Bal E, Pei XY, Madrange M, Khelil A, Sahel H, et al. IL36RN mutations affect protein expression and function: a basis for genotype–phenotype correlation in pustular diseases. J Invest Dermatol 2016; 136: 1811–1819.

118. Hussain S, Berki DM, Choon SE, Burden AD, Allen MH, Arostegui JI, et al. IL36RN mutations define a severe auto-inflammatory phenotype of generalized pustular psoriasis. J Allergy Clin Immunol 2015; 135: 1067–1070.e1069.

119. Setta-Kaffetzi N, Navarini AA, Patel VM, Pullabhatla V, Pink AE, Choon S-E, et al. Rare pathogenic variants in IL36RN underlie a spectrum of psoriasis-associated pustular phe-notypes. J Invest Dermatol 2013; 133: 1366–1369.

120. Setta-Kaffetzi N, Simpson MA, Navarini AA, Patel VM, Lu HC, Allen MH, et al. AP1S3 mutations are associated with pustular psoriasis and impaired Toll-like receptor 3 traf-ficking. Am J Hum Genet 2014; 94: 790–797.

121. Guo Y, Chang C, Huang R, Liu B, Bao L, Liu W. AP1 is essen-tial for generation of autophagosomes from the trans-Golgi network. J Cell Sci 2012; 125: 1706–1715.

122. Hussey S, Travassos LH, Jones NL. Autophagy as an emer-ging dimension to adaptive and innate immunity. Semin Immunol 2009; 21: 233–241.

123. Lee HM, Shin DM, Yuk JM, Shi G, Choi DK, Lee SH, et al. Autophagy negatively regulates keratinocyte inflammatory responses via scaffolding protein p62/SQSTM1. J Immunol 2011; 186: 1248–1258.

124. Mahil SK, Twelves S, Farkas K, Setta-Kaffetzi N, Burden AD, Gach JE, et al. AP1S3 mutations cause skin auto-inflammation by disrupting keratinocyte autophagy and up-regulating IL-36 production. J Invest Dermatol 2016; 136: 2251–2259.

125. Mossner R, Frambach Y, Wilsmann-Theis D, Lohr S, Jacobi A, Weyergraf A, et al. Palmoplantar pustular psoriasis is associated with missense variants in CARD14, but not with loss-of-function mutations in IL36RN in European patients. J Invest Dermatol 2015; 135: 2538–2541.

126. Viguier M, Guigue P, Pages C, Smahi A, Bachelez H. Suc-cessful treatment of generalized pustular psoriasis with the interleukin-1-receptor antagonist Anakinra: lack of correlation with IL1RN mutations. Ann Intern Med 2010; 153: 66–67.

127. Huffmeier U, Watzold M, Mohr J, Schon MP, Mossner R. Successful therapy with anakinra in a patient with gene-ralized pustular psoriasis carrying IL36RN mutations. Br J Dermatol 2014; 170: 202–204.

128. Tauber M, Viguier M, Le Gall C, Smahi A, Bachelez H. Is it relevant to use an interleukin-1-inhibiting strategy for the treatment of patients with deficiency of interleukin-36 receptor antagonist? Br J Dermatol 2014; 170: 1198–1199.

129. Mahil SK, Catapano M, Di Meglio P, Dand N, Ahlfors H, Carr IM, et al. An analysis of IL-36 signature genes and individuals with IL1RL2 knockout mutations validates IL-36 as a psoriasis therapeutic target. Sci Transl Med 2017; 9.

130. Bachelez H, Choon SE, Marrakchi S, Burden AD, Tsai TF, Morita A, et al. Inhibition of the Interleukin-36 pathway for the treatment of generalized pustular psoriasis. N Engl J Med 2019; 380: 981–983.

131. Chandra A, Senapati S, Ghosh S, Chatterjee G, Chatterjee R. Association of IL12B risk haplotype and lack of interac-tion with HLA-Cw6 among the psoriasis patients in India. J Hum Genet 2017; 62: 389–395.

132. Hirata J, Hirota T, Ozeki T, Kanai M, Sudo T, Tanaka T, et al. Variants at HLA-A, HLA-C, and HLA-DQB1 confer risk of psoriasis vulgaris in Japanese. J Invest Dermatol 2018; 138: 542–548.

133. Al-Mamari F, Al-Shirawi A, Banodkar D, Al-Hashmi S, Al-Yahyaae F, Varghese M, et al. HLA antigens in Omani psoriasis vulgaris patients. Oman Med J 2009; 24: 27–29.

134. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol 2013; 133: 377–385.

135. Morris AP. Transethnic meta-analysis of genomewide as-sociation studies. Genet Epidemiol 2011; 35: 809–822.

136. 1000 Genomes Project Consortium. A global reference for human genetic variation. Nature 2015; 526: 68–74.

137. Degenhardt F, Wendorff M, Wittig M, Ellinghaus E, Datta LW, Schembri J, et al. Construction and benchmarking of a multi-ethnic reference panel for the imputation of HLA class I and II alleles. Hum Mol Genet 2019; 28: 2078–2092.

138. Malik R, Chauhan G, Traylor M, Sargurupremraj M, Okada Y, Mishra A, et al. Multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes. Nat Genet 2018; 50: 524–537.