Genome Medicine

Review

Genetic susceptibility to psoriasis: an emerging picture

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Abstract

Psoriasis is recognized as a complex disease for which multiple genetic and non-genetic factors influence susceptibility. The major susceptibility locus resides in the MHC class I region and, until relatively recently, evidence for non-MHC loci was inconsistent. Like many common diseases, knowledge of the genetic basis of this condition has been advanced dramatically in recent times with the advent of genome-wide association studies using single nucleotide polymorphisms. Here, we give an overview of current knowledge of genetic risk factors for psoriasis and consider emerging studies that may further add to our understanding of the genetic basis of the disease.

Introduction

Psoriasis is a chronic immune-mediated skin disease that affects approximately 2% of the population worldwide [1]. Most cases (75%) of chronic plaque psoriasis first present before the age of 40 years - known as early-onset or type I psoriasis - and late-onset cases presenting after the age of 40 years are classified as type II psoriasis [2]. The higher concordance rate in monozygotic twins (65 to 73% compared with 15 to 30% for dizygotic twins) suggests that psoriasis is a typical complex disease in which both genetic and environmental factors influence susceptibility [3-6]. Family-based analyses of patients with psoriasis and numerous population-based epidemiological studies have also confirmed the genetic basis of the disease [5,7-12]. From such studies, the heritability of psoriasis (a measure of the proportion of variability of a trait that is due to genetic factors) has been estimated to be 60 to 90% in the Caucasian population [10] and as high as 90 to 100% among Danish twins [13].

The importance of genes in psoriasis has long been recognized, and traditional approaches of family-based linkage studies and population-based candidate gene association studies have had some success in identifying genetic risk factors. Although psoriasis was not in the first wave of ground-breaking single nucleotide polymorphism (SNP)-based genome-wide association studies (GWASs), which have signaled a new era in the identification of common variants determining susceptibility to common diseases, this approach is now being applied and it is timely to review current knowledge of psoriasis genetics. As evidenced by studies in other conditions, such as Crohn's disease, for which the key role of autophagy has been discovered using GWASs [14-16], advances in our understanding of the genetic markers involved in the phenotypic expression of this complex disorder will be crucial in providing the next generation of therapeutic targets for psoriasis.

Psoriasis susceptibility loci identified before genome-wide association studies

More than 35 years ago, associations with markers within the major histocompatibility complex (MHC) region on chromosome 6 were first identified for psoriasis [17] and, to this day, this locus remains the major susceptibility locus for psoriasis, accounting for 35 to 50% of Caucasian genetic susceptibility to early-onset psoriasis [18-20]. Strong associations have been found between familial psoriasis and human leukocyte antigen (HLA) class I genes, predominately *HLA-Cw6*, with a prevalence of up to 85% in early-onset patients compared with 15% in late-onset psoriasis and approximately 10% in the general population [2]. A consistent finding of linkage studies carried out in families with psoriasis was a broad peak over the MHC, designated *PSORS1*, leading to speculation that the locus could harbor effects additional to those already identified for *HLA-Cw6*. The strong linkage disequilibrium across this region adds to the difficulties of fine mapping and determination of causal effects. Uncertainty remains as to whether *HLA-Cw6* is the causal variant, with other studies implicating different genes [21-24]. Recent evidence seems again to favor a role for *HLA-Cw6* in both Caucasians [25] and Chinese families [26], but conditional analysis demonstrated that, although *HLA-Cw6* was a major risk allele, it does not fully account for the *PSORS1* linkage evidence.

GWAS, genome-wide association study; LD, linkage disequilibrium; MAF, minor allele frequency; MHC, major histocompatibility complex; *PSORS1-PSORS7*, psoriasis susceptibility loci identified in genome-wide linkage studies; SNP, single nucleotide polymorphism.

Whole-genome linkage screens of psoriasis [27-36] identified many potential susceptibility loci but, with the possible exception of *PSORS1*, fine mapping of these loci did not reveal convincing evidence for disease susceptibility genes, almost certainly because the studies were under-powered and many of the linkages were false positives. In contrast, recent well powered candidate gene association studies have been more fruitful. Notable successes include the replication of SNPs identified in the protein tyrosine phosphatase gene *PTPN22* (rs3789604) [37], the asthma susceptibility gene *ADAM33* (rs597980) [38,39] and in the kinase-associated protein *CDKAL1* (rs6908425) [40] in a large US Caucasian cohort of 1,448 psoriasis patients and 1,385 controls [41]. Furthermore, strong association has also been reported between the interleukin gene *IL15* and the disease in the Chinese Han population (g.596516, $P = 5 \times 10^{-6}$) [42]. Interestingly, this polymorphism is not associated with psoriasis in any of the UK [43], German [44] or US Caucasian populations [41] investigated, and the minor allele frequency (MAF) for this SNP and others across *IL15* differs quite strikingly between the populations, suggesting heterogeneity in the genetic suscep-tibility to psoriasis.

As well as being investigated for any potential functional role in the pathogenesis of psoriasis, candidates are increasingly targeted following association with related diseases. Although the *MHC* locus has long been known to harbor the major susceptibility region for many inflam-matory and autoimmune diseases, it is increasingly becoming apparent that psoriasis shares other non-*MHC* susceptibility loci with diseases such as type I diabetes and multiple sclerosis [45]. Of particular interest for psoriasis because of its co-morbidity with the disease are the regions of susceptibility shared with Crohn's disease. The preva-lence of psoriasis is reported to be 9.6% among those affected with the chronic inflammatory bowel disease, compared with 2.2% of the controls [46]. Some recent candidate gene studies of psoriasis have adopted the approach of targeting reported Crohn's disease associations and have revealed many overlapping genetic loci common in both diseases [15,40]. One of these studies investigated 15 established Crohn's disease susceptibility loci in 1,256 psoriasis patients and 2,938 unrelated healthy controls. The same SNPs at three of these loci, 1q24, 6p22 (the *CDKAL1* gene also associated with type II diabetes) and 21q22 [40], were significantly associated with psoriasis, with very similar effect sizes and the same risk alleles as those with Crohn's disease [14,47].

In addition to the well validated findings described above, there have been many conflicting reports of association and a frequent failure in replicating initial observations from candidate gene studies, probably reflecting low sample sizes and, therefore, low power to detect what are likely be relatively modest or weak effects. Candidate gene studies may also be considered to be limited as they tend to be hypothesis driven and based on existing knowledge of the disease and its pathogenesis. More recently, the technological advances that allow the high-throughput, accurate, simultaneous genotyping of hundreds of thousands of SNPs has bought a new era of genetic studies in which the whole genome can be systematically screened in a hypothesis-free manner, with the potential to uncover novel susceptibility markers in GWASs.

Psoriasis susceptibility loci identified by genome-wide association studies

The GWAS has recently become an extensively used approach as a result of advances in affordable high-throughput SNP genotyping technology and the availability of large patient cohorts and information on over four million validated SNPs with MAFs of at least 1%, which are all publicly available on the HapMap database [48]. The HapMap Project also describes patterns of linkage disequilibrium (LD) between common polymorphisms across the genome, which crucially allows subsets of tagSNPs to be designed, ensuring that common variants will either be directly assayed or strongly correlated with an allele of a single tagSNP or tagSNP haplotype.

So far, four psoriasis GWASs have been reported in Caucasian populations [49-52], which have all identified novel psoriasis loci and validated established associations, with MHC- based SNPs in the proximity of the *HLA-C* region proving most significant. The main findings of the first psoriasis GWAS, involving 1,446 US patients and 1,432 controls, reported association with four variants mapping to two non-MHC genes from the genotyping of 25,215 gene-centric SNPs: *IL12B* on chromosome 5q and *IL23R*, a gene encoding an interleukin receptor, on chromosome 1p of the broad *PSORS7* locus, identified in early studies [30,50].

Subsequent replication studies and more recent GWASs [49-53] have confirmed *IL12B* and *IL23R* as non-MHC genes associated with psoriasis risk. Furthermore, these polymorphisms have been investigated in studies of other diseases, with positive associations reported for inflam-matory bowel disease [49,54], psoriatic arthritis [51], atopic dermatitis [55], asthma [51,56] and ankylosing spondylitis [57,58] but no association found with others, such as multiple sclerosis [59] and rheumatoid arthritis [60,61]. Indeed, the association of *IL12B* and *IL23R* with psoriasis has been strongly supported by the observation of increased IL23 in plaques of psoriasis and induction of psoriatic hyperplasia by injection of IL23 into mouse skin. The potential benefits of blocking the effects of the IL12 and IL23 cytokines have been clearly demonstrated, with the human monoclonal antibody ustekinumab found to be an effective treatment for severe psoriasis [62]. Two recently completed large randomized, double-blind, placebo-

controlled clinical trials (PHOENIX I and II) of ustekinumab have demonstrated its effectiveness for treatment of moderate-to-severe psoriasis patients for up to 52 weeks [63] and 72 weeks of treatment [64]. Although the precise mechanism by which polymorphisms in *IL12B* and *IL23R* influence the disease process still requires further clarification, the associations and functional evidence suggest that the IL12/IL23 pathway has a key role in the pathogenesis of psoriasis.

The UK GWAS of 408,000 SNPs in an initial 318 psoriasis patients and 288 controls, followed by a validation stage using a further 519 patients and 528 controls, detected a novel association with a cluster of six correlated variants on chromosome 20q13 encompassing the transcription factor gene *ZNF313* [65]. One of these variants, rs495337, was subsequently validated in two independent replication sets of German and UK populations [65] with functional evidence supporting a role for *ZNF313* as a novel psoriasis susceptibility gene [65]. An independent GWAS of both psoriatic arthritis and psoriasis patients also reported novel susceptibility loci for psoriasis [51]. Genotyping 311,398 SNPs in an initial 223 US psoriasis patients and 519 Northern European controls, several novel associations were detected and validated in 577 US psoriasis patients and 737 controls. Polymorphisms in the gene encoding the Golgi complex protein COG6, the epidermal differentiation complex region of *PSORS4*, and a region on chromosome 15q21 all demonstrated strong evidence of association with psoriasis [51]. Recently, a US GWAS of 1,409 psoriasis cases and 1,436 controls, followed up in 5,048 patients and 5,041 controls, has reported further novel loci at *IL23A*, the zinc finger protein gene *TNFAIP3*, the TNFAIP3-interacting protein gene *TNIP1*, *IL13* and *IL4*, suggesting a key role for NF-κB regulation and T-helper2 cells in psoriasis [52].

Further to these studies, the first large GWAS undertaken in a Chinese cohort (initial cohort: 1,139 cases and 1,132 controls; validation cohort: 5,182 cases and 6,516 controls) replicated the associations with MHC and *IL12B* and detected a novel signal within the late cornified envelope (LCE) gene cluster on chromosome 1q21, which encodes key proteins implicated in epidermal terminal differentiation [66]. In conclusion, GWASs have been key in identifying common novel variants and validating existing polymorphisms of large or modest effect size that have been associated with psoriasis. With a large psoriasis cohort forming part of the Wellcome Trust Case Control Consortium [67] Phase II program, and results expected later this year, it is anticipated that further novel and validated associations will be reported for the disease.

Copy number variants

Following on from the abundance of GWAS data generated by SNP-based analysis, recent attention has switched to the variation of gene copy number across the genome, as it is increasingly becoming apparent that associations with common SNPs are unlikely to fully account for genetic susceptibility to complex diseases. Measuring the differences in copy number is complex, with many different types of variation possible, such as insertions and deletions. Consequently, much work is currently focused on refining this technology and characterizing the probes for these variants, so that they can be accurately detected and analyzed. Despite this, psoriasis is one disease in which associations have already been established with copy number variants. One study reported that an increased copy number of the β-defensin gene cluster on chromosome 8, targeted because of its function of encoding antimicrobial peptides in the innate immune response - a key component of psoriasis pathogenesis - was associated with a significantly increased risk of the disease. This was demonstrated in independent Dutch and German psoriasis cohorts [68]. Furthermore, a linear regression conducted by the authors [68] on the combined cohorts used in the study suggested that each additional copy of the β-defensin gene cluster above two copies significantly increased relative risk by 34%.

Another association between copy number variation and the disease has very recently been reported on chromosome 1q21, within the defined *PSORS4* locus encompassing the late cornified envelope genes *LCE3B* and *LCE3C*. A deletion of a region containing these genes was found to be associated with a significantly increased risk of psoriasis. This finding was further supported by single-point analysis of SNP rs4112788, which is in strong LD with the deletion and which also showed strong evidence of association with the disease [69].

Conclusions

GWASs have undoubtedly been a major breakthrough in investigating the genetic predisposition to complex disease, with hundreds of thousands of SNPs being genotyped in large sample sizes exceeding those for any previous methodology. Consequently, with statistical power greatly increased and study design further optimized, GWASs are unquestionably the preferred approach for investigating the genetics of complex diseases such as psoriasis, with rapid progress anticipated in the identification of susceptibility genes and loci. However, substantial replication and validation studies will be crucial in establishing these associations as risk factors for psoriasis. Larger cohorts will be pivotal for increasing power in identifying and validating causal variants of high and modest effect size. Furthermore, rare variants and small effect sizes underpinning genetic susceptibility of psoriasis will remain mostly undetected until sufficiently well powered studies are available, which will be achievable only through meta-analyses from extensive collaborations. Following on from this, the major challenge will be to identify the casual variants from these numerous association signals. Current

strategies for this include re-sequencing and fine mapping using known and newly identified SNPs. The need for this may be reduced in the near future as efforts such as the 1000 Genomes Project [70] continue to add to our knowledge of human variation. These projects continue to drive technologies forward and costs down such that, in the not too distant future, strategies for the characterization of genetic risk factors for common disease may be based on genome-wide re-sequencing.

Knowledge of the genetic basis of psoriasis has advanced considerably in the past few years and looks set to continue at a great pace. The likely impact on treatment of patients with this condition is only beginning to be realized, but links between effective therapies and genetic associations are already emerging. For patients with severe psoriasis, there are two main treatment options, the immunosuppressive drugs such as methotrexate and the newer biological agents that target tumor necrosis factor alpha (TNF-α), IL12/23 or T-cell migration. Recent data have suggested that it may be possible to target the use of methotrexate depending on genotype in psoriasis and rheumatoid arthritis patients [71,72]. The impressive efficacy of ustekinumab (effective in 70% of patients at 12 weeks), which inhibits IL12/23, shows the enormous potential for targeting genetic loci discovered as part of GWASs and also indicates that loci that may seem to account for only a small amount of the total genetic variation of a condition can still be enormously effective when targeted as a treatment. A second drug that inhibits IL12/23 is ABT 874, which is currently undergoing phase III trials and shows early promise. Thus, we can look forward to a future of new and improved therapies administered in a targeted manner to individuals genetically predisposed to benefit from them.

Competing interests

RBW has been a consultant to or speaker for Abbott, Janssen Cilag, Merck Serono, Schering Plough and Wyeth, all of which manufacture biological drugs for psoriasis. CEMG has been a paid advisor to and/or has received research grants from Abbott, Janssen-Cilag, Leo, Merck-Serono, Novartis, Pfizer, UCB Pharma and Wyeth, all of which manufacture drugs used in the treatment of psoriasis. The other authors declare that they have no competing interests.

Authors' contributions

RLS is lead author of this review.

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