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Psoriasis and susceptibility to other autoimmune diseases: an outline for the clinician

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Faisal R Ali

*Dermatology Centre, University of Manchester, Salford
Royal NHS Foundation Trust,
Manchester Academic Health
Science Centre, Manchester
M6 8HD, UK*



Richard B Warren

*Author for correspondence:
Dermatology Centre, University of Manchester, Salford
Royal NHS Foundation Trust,
Manchester Academic Health
Science Centre, Manchester,
M6 8HD, UK
Tel.: +44 161 206 4344
Fax: +44 161 206 1095
richard.warren@manchester.ac.uk*

Psoriasis is a chronic inflammatory disease affecting 2% of the adult population. Common cutaneous manifestations include well-defined red plaques with a silvery-white scale, typically distributed symmetrically on extensor surfaces [1]. The multisystem nature of psoriasis, namely its association with a seronegative arthropathy and the metabolic syndrome, is now well established. During the last decade, it has become increasingly recognized that psoriasis is part of an autoimmune spectrum in which diverse diseases share common underlying genetic susceptibility loci, molecular mechanisms and treatment modalities. We will review existing evidence and explore the implications this may have to the practicing clinician.

Past

Epidemiological studies have informed putative examples of autoimmune links with psoriasis. Up to 30% of patients with cutaneous psoriasis suffer from concomitant psoriatic arthritis [2], a deforming seronegative arthropathy that may manifest as a polyarthritis, sacroileitis, monoarthritis or arthritis mutilans. It has also been noted that there is an increased prevalence of rheumatoid arthritis [3], celiac disease [4] and Crohn's disease [5] in patients with psoriasis, and there is general recognition that sufferers of one autoimmune disease are predisposed to others.

Present: genetic studies

Recent advances in genetic technologies now permit the systematic interrogation

of millions of markers scattered across the genome comparing their frequencies between the general population and diseases such as psoriasis. The advent of such genome-wide association studies (GWAS) has uncovered many novel associations of diseases. At least 36 genetic loci are now known to be associated with psoriasis, divided into four principal categories: innate immunity, T-cell signaling, skin barrier function and NF-κB signaling [6,7].

These genetic studies have underlined the pan-autoimmune theorem, which purports that individuals with one autoimmune disease are predisposed genetically to other autoimmune diseases, and supports existing epidemiological data.

This characteristic has been exploited to help unearth the genetics of psoriasis. By systematically searching for known genetic risk variants associated with a range of autoimmune diseases in a cohort of psoriasis patients, researchers have recently detected novel associations of early-onset psoriasis with IL-2/21, which are cytokines implicated in T-cell homeostasis, activation and proliferation [8]. Similar systematic interrogation of known rheumatoid arthritis loci has facilitated validation of the *REL* locus in psoriasis and psoriatic arthritis patients [9,10]. *REL* encodes c-Rel, one of the members of the NF-κB family, transcription factors involved in the inflammatory response and regulation of cell survival.

Curiously, susceptibility to certain autoimmune diseases appears to impart protection to others, one such example being the *REL* locus that predisposes to psoriasis [11],

yet protects from development of rheumatoid arthritis [12]. The minor allele of the *PTPN22* allele imparts susceptibility to rheumatoid arthritis, Type 1 diabetes and autoimmune thyroid disease, yet affords protection from Crohn's disease [13]. Taken together, these findings indicate clustering of autoimmune diseases, with antibody-mediated autoimmune diseases and autoimmune diseases associated with seronegative arthritides forming distinct groups, with presumed distinct underlying molecular pathways [10]. It is noteworthy that a different single nucleotide polymorphism within the same genetic locus may associate with different diseases, as demonstrated by the *PTPN22* locus. *PTPN22* encodes a protein tyrosine phosphatase that modulates responsiveness of lymphoid tissue. The R620W polymorphism imparts susceptibility to several autoimmune diseases but not to psoriasis [14,15], while two additional single nucleotide polymorphisms at the *PTPN22* locus are found to be psoriasis risk alleles [16].

Present: implications for the clinician

During consultation, it is often instructive for physicians to interrogate patients with psoriasis about personal and family history of other autoimmune conditions. In the UK guidelines [17], it is recommended that all psoriasis patients should be screened for psoriatic arthritis using a validated instrument such as the Psoriasis Epidemiological Screening Tool [18], as timely treatment of psoriatic arthritis stems development of incurable, deforming disease. Close liaison between dermatology and rheumatology teams (e.g., in shared care psoriasis–psoriatic arthritis clinics) will help to ensure that an individual patient is taking the optimal therapy to hamper disease progression [2].

Future

While GWAS have disclosed many new genetic associations of psoriasis, our understanding of causative mutations remains incomplete. The phenomenon of linkage disequilibrium, in which adjacent sections of the genome appear to be inherited together, prevents us from definitively attributing mutations of a particular base pair to susceptibility to psoriasis. This is exemplified by the well-recognized *PSORS1* susceptibility region that encodes HLA-C [6]. Future work will be focused around fine mapping of such autoimmune susceptibility regions to better inform our understanding of precise causation.

There will also be a commensurate increase in functional studies of associated molecular pathways in the pathogenesis of psoriasis to provide further therapeutic strategies. For example, IL-17, identified by GWAS as being strongly associated with psoriasis, has been successfully targeted by monoclonal antibodies in promising Phase II trials [19,20].

Furthermore, our greater understanding of pharmacogenetics, the relationship between genetic susceptibility markers and response to therapy, will usher in a new era of stratified medicine, in which an individual's genetic profile will be used to guide initial therapy to both maximize efficacy and reduce the likelihood of toxicity [21].

As greater numbers of patients with psoriasis are treated with systemic and biologic agents, our epidemiological knowledge of the safety and longer-term side effects of such medications will increase. In the next 5–10 years psoriasis-specific data will be available from dermatologic registries, such as the British Association of Dermatologists Biologics Interventions Register [22].

Conclusion

Future investigations will affirm the prominence of psoriasis as a disease impacting upon many systems, superseding its former status as a disease of the skin. As our understanding of the genetics of psoriasis and related autoimmune conditions grows, it becomes increasingly evident that some individuals are genetically predisposed to a plethora of phenotypically diverse autoimmune diseases. In the impending era of precision medicine, we envisage an environment in which therapies will be matched to an individual's genotypic or phenotypic signature to maximize efficacy and reduce the likelihood of toxicity. The dermatologists and internists of the 21st century will not only have to take care of dermatological manifestations of psoriasis, but also the associated malaises of other bodily systems.

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