Genetic susceptibility to psoriasis and psoriatic arthritis: implications for therapy

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Summary

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Psoriasis is a complex genetic disease whose inheritance is not explained by simple Mendelian genetics, but rather arises due to the interaction of multiple genetic and environmental factors.¹ Recent advances in genotyping technology have facilitated genome-wide association studies (GWAS), which in a short period of time have identified many genetic markers associated with psoriasis and highlighted novel mechanistic pathways. A greater understanding of the pathophysiological pathways causing psoriasis may provide future therapeutic targets and be of prognostic value in determining which treatment will be most effective in subsets of patients.

Psoriatic arthritis (PsA) is a condition that affects approximately 30% of people with psoriasis.² Such patients have the clinical characteristics of psoriasis in addition to arthritis, soft-tissue swelling and enthesitis and, as with psoriasis, family studies have suggested a strong genetic component to the disease.^{3,4}

In this review, we discuss the known genetic associations with psoriasis susceptibility, including findings from recent GWAS, and compare genetic risk factors in psoriasis with those of PsA. We also summarize the results of studies under-

The era of genome-wide association studies has revolutionized the search for genetic susceptibility loci in complex genetic conditions such as psoriasis. There are currently 16 loci with confirmed evidence for association with psoriasis susceptibility but there is the potential for more to be discovered as the genetic heritability of the disease has not yet been fully explained. Many of the associated loci overlap with those for psoriatic arthritis. In contrast to psoriasis susceptibility, few studies have been performed to identify predictors of drug response in psoriasis. As large-scale collaborations and registries for psoriasis and psoriatic arthritis are established, it is likely that a genome-wide approach may be used as a more effective method of searching for genetic predictors of treatment response. However, candidate gene studies will still have a role; for example, it is likely that some disease susceptibility genes will also be markers of treatment response, based on evidence from other diseases. This review summarizes recent advances in investigating the role genetics plays in psoriasis susceptibility and contrasts these to advances made in psoriatic arthritis. Further, it describes the genetics of treatment response in the two diseases and indicates how susceptibility loci could be used to identify drug response in the future.

taken to identify genetic predictors of drug response in both psoriasis and PsA.

Genetics of psoriasis

Psoriasis susceptibility region 1

The first genetic association studies in psoriasis were carried out in 1972 and were focused on the major histocompatibility complex (MHC) region on chromosome 6.^{5,6} Subsequently, human leukocyte antigen C (HLA-C) has been consistently shown to be associated with psoriasis.^{7–18} The 80–200-kb susceptibility region contained therein, designated psoriasis susceptibility region 1 (PSORS1), was identified through linkage studies.^{19–21} Two genes have been proposed as candidates for PSORS1. A C > T polymorphism at position +1243 in corneodesmosin (CDSN) was reported to be associated with psoriasis in 1999.²² In the same year, PSORS1 was narrowed to a region 89–200 kb telomeric of HLA-C with coiled-coil α -helical rod protein 1 (CCHCR1) as another possible candidate.²¹ Recent evidence suggests that HLA-C is the

most likely causative gene for psoriasis.²³ However, this should be interpreted with caution as the use of selected single nucleotide polymorphisms (SNPs) in association studies and the presence of linkage disequilibrium between markers have made the identification of the causative mutation in PSORS1 difficult.

Subgroups of psoriasis are genetically heterogeneous for PSORS1. While early-onset psoriasis (onset before age 40 years) and guttate psoriasis²⁴ are strongly associated with PSORS1, late-onset psoriasis (onset after age 40 years) appears not to be associated.²⁵

Genome-wide association studies

Recent advances allowing rapid genotyping of hundreds of thousands of SNPs distributed across the genome have led to the advent of GWAS.^{26,27} Such GWAS do not rely upon prior hypotheses as to underlying molecular pathways and have been able to identify novel candidate genes and mechanisms associated with psoriasis. The GWAS performed thus far have all confirmed the association of PSORS1 with psoriasis but have also identified novel genetic loci containing candidate genes involved in the adaptive and innate immune responses and barrier integrity. Table 1 summarizes the genetic loci associated with psoriasis identified to date.

A number of important lessons can be drawn from these studies with regard to the pathways that contribute to disease (Fig. 1). Firstly, antigen presentation to the adaptive immune system by the innate immune system appears of paramount importance in triggering disease. This is supported by the fact that HLA-Cw6 remains the largest genetic susceptibility factor for psoriasis. Furthermore, the more recently identified endoplasmic reticulum aminopeptidase 1 (ERAP1) gene has been shown to interact with HLA-C, and is thought to regulate the antigenic peptides that bind to HLA-C.^{18,28}

Secondly, the candidate genes identified from GWAS provide clues to the key inflammatory pathways underlying psoriasis. For example, the psoriasis-associated genes tumour necrosis factor alpha-induced protein 3 (TNFAIP3), TNFAIP3-interacting protein 1 (TNIP1), v-rel reticuloendotheliosis viral oncogene homolog (REL), tyrosine kinase 2 (TYK2), TRAF3-interacting protein 2 (TRAF3IP2) and nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor-alpha (NFKBIA) are all regulators of the nuclear factor (NF)- κ B pathway.^{14,16,18,29} NF- κ B is a transcription factor involved in the regulation of the innate immune system and apoptosis. The TNFAIP3 protein product, A20, inhibits NF- κ B and also interacts with TNIP1, thereby inducing keratinocyte hyperproliferation seen in psoriasis. Another key pathway involves the interleukin (IL)-23 signalling pathway, which regulates Th17-cell activation. Variants within the genes, IL12B, IL23R and IL23A are all strongly associated with psoriasis susceptibility along with ZNF313/RNF114, which is also involved in T-cell activation.^{14,17,18,26,27,30} Activated Th17 cells produce IL-17, which in turn can activate the NF κ B pathway via the ACT1

protein, which is encoded by another psoriasis susceptibility gene, TRAF3IP2.^{13,16}

Thirdly, GWAS results have also provided clues to the mechanism by which the psoriasis phenotype is triggered in genetically susceptible individuals. For example, LCE3A, LCE3C and LCE3D in the late cornified envelope (LCE) gene cluster have been strongly associated with psoriasis and have important roles in skin barrier function.¹⁵ Candidate gene studies have also implicated the β -defensin gene cluster on chromosome 8; β -defensins are antimicrobial peptides secreted in the epidermis to protect against microbial invasion.³¹ These clues from GWAS help to conceptualize how psoriasis may be triggered. Thus, impaired skin barrier function may allow an infectious pathogen or antigen to enter the body, be ingested and processed by antigen-presenting cells and presented to Th17 cells of the immune system. The association of both ERAP1 and HLA-Cw6 support the role of antigen presentation but whether this is an autoantigen or a foreign peptide, such as from a microbe, is unclear. The gene interferon induced with helicase C domain 1 (IFIH1), which has been associated with psoriasis in one GWAS,¹⁸ encodes a protein that mediates induction of interferon response to viral RNA, suggesting that at least one trigger may be viral.¹⁸ It is known that interferon- α either induces or greatly exacerbates existing psoriasis when administered to patients being treated for conditions such as renal cancer^{32–35} and that it is upregulated in response to viral infection.^{36,37} In individuals genetically predisposed to psoriasis, the immune system is already primed and it is possible that activation by interferon may lead to development of the classical psoriasis phenotype.

Results of GWAS are also allowing some exploration of the genetic similarities and differences between psoriasis and PsA. While there have been fewer GWAS of PsA, it is clear from candidate gene studies that many psoriasis susceptibility loci are also associated with PsA. The allele HLA-Cw6 appears to be a common susceptibility gene for psoriasis and PsA in that it is found more commonly in both conditions than in healthy controls. Interestingly, however, it has a significantly higher frequency in psoriasis-only patients than those with PsA and has been associated with a less severe phenotype of PsA.¹² The IL12B, IL23A, IL23R, LCE and TNIP1 gene variants are further examples of psoriasis susceptibility genes that have also been found to associate with PsA.^{12,38–40}

Some genes appear to be associated only with PsA and not with psoriasis. Several candidate gene studies have reported that the HLA-B27 antigen is associated with PsA but not psoriasis.^{41,42} IL2 and IL21 were originally reported to be associated with PsA but not with psoriasis in a small GWAS by Liu *et al.*;¹² however, a recent study has also reported association with psoriasis.⁴³ Replication is required to establish if IL2 or IL21 confer susceptibility to either or both diseases. Association with the IL13 gene was originally reported in two psoriasis GWAS;^{14,18} subsequent analysis in one showed that the primary association was with PsA, and two further studies in which psoriasis and PsA samples were analysed also showed an association with PsA but not with psoriasis.^{44,45} Hence,

Table 1 Psoriasis (Ps) and psoriatic arthritis (PsA) associated genes

Gene	Chromosomal region	Ps or PsA	Genetic marker	P-value	Odds ratio (95% CI)	Reference
ERAP1	5q15	Ps	rs151823	9.32×10^{-9}	0.89 (0.85–0.92)	28
			rs27524	2.56×10^{-11}	1.13 (1.05–1.22)	18
HLA-C	6p21	PsA	rs13191343	2.32×10^{-72}	2.37 (2.16–2.61)	16
			rs10484554	6.86×10^{-11}	2.4 (1.8–3.1)	12
			rs2395029	1.86×10^{-10}	3.2 (2.2–4.6)	
		Ps	rs10484555	1.81×10^{-39}	2.8 (2.4–3.3)	
			rs2395030	2.13×10^{-26}	4.1 (3.1–5.3)	
			rs12191877	$< 10^{-100}$	2.64 ^a	14
			rs1265181	1.93×10^{-208}	22.62 ^a	15
			rs10484554	4.06×10^{-214}	4.66 (4.23–5.13)	18
			rs12191877	4.21×10^{-32}	2.79 (2.35–3.33)	13
			rs3134792	1×10^{-9}	n/a ^b	17
IFIH1	2q24	Ps	rs17716942	1.06×10^{-13}	1.29 (1.17–1.43)	18
IL2/IL21	4q26–27	PsA	rs13151961	1.6×10^{-3}	0.64 (0.49–0.84)	12
			rs7684187	1×10^{-3}	0.72 (0.59–0.87)	
			rs6822844	8×10^{-3}	0.72 (0.56–0.92)	
			rs6840978	0.013	0.77 (0.62–0.95)	
IL12B	5q31–33	Ps	rs3212227	7.85×10^{-10}	0.64 (0.56–0.73)	26
			rs6887695	4.08×10^{-8}	0.70 (0.63–0.79)	
			rs10045431	1×10^{-4}	1.41 (1.21–1.64)	27
			rs3212227	0.036	0.76 (0.63–0.92)	
			rs7709212	6×10^{-3}	0.76 (0.65–0.89)	
			rs2082412	2×10^{-28}	1.44 ^a	14
			rs3213094	2.58×10^{-26}	0.78 (0.74–0.81)	15
			rs7709212	1.12×10^{-20}	0.80 (0.77–0.84)	
			rs2546890	1.29×10^{-20}	n/a ^b	13
			rs953861	6.21×10^{-18}	n/a ^b	
			rs3213094	4.93×10^{-11}	1.39 (1.26–1.53)	18
			rs6887695	5×10^{-5}	n/a ^b	12
		PsA	rs6887695	1.3×10^{-3}	0.69 (0.56–0.85)	
			rs12188300	7.33×10^{-17}	1.70 (1.50–1.93)	16
			rs3212227	1×10^{-3}	1.43 (1.17–1.76)	39
			rs6887695	4.2×10^{-5}	1.43 (1.18–1.74)	
IL13	5q31	Ps	rs20541	5×10^{-15}	1.27 ^a	14
				0.0232	1.12 (1.02–1.24)	18
		PsA	rs1800925	6.1×10^{-5}	1.33 (1.16–1.53)	45
			rs20541	8×10^{-4}	1.27 (1.10–1.45)	
IL23A	12q13	Ps	rs2066808	1×10^{-9}	1.34 ^a	14
		PsA	rs2066808	9.05×10^{-7}	0.54 (0.43–0.70)	40
IL23R	1p31	Ps	rs7530511	0.014	0.78 (0.66–0.91)	26
			rs11209026	1.89×10^{-4}	0.63 (0.50–0.79)	
			p.Arg381Gln	1.4×10^{-4}	0.49 (0.35–0.68)	27
			rs2201841	3×10^{-8}	1.13 ^a	14
			rs11209026	7.13×10^{-7}	1.49 (1.27–1.74)	18
			rs11209026	1.4×10^{-4}	0.56 (0.41–0.76)	12
		PsA	rs11209026	8.3×10^{-4}	0.52 (0.35–0.77)	
			rs11209026	0.04	1.40 (1.01–1.96)	39
IL28RA	1p36	Ps	rs4649203	6.89×10^{-8}	1.13 (1.05–1.22)	18
LCE	1q21	Ps	rs6701216	6.2×10^{-5}	1.45 (1.21–1.75)	12
			rs4112788	7.13×10^{-27}	0.77 (0.74–0.81)	15
			rs4085613	6.69×10^{-30}	0.76 (0.72–0.80)	
			rs4845454	4.35×10^{-29}	0.76 (0.72–0.80)	
			rs1886734	2.18×10^{-28}	0.76 (0.73–0.80)	
			rs4112788	3.32×10^{-10}	1.29 (1.19–1.40)	18
			LCE3B/C del	3.8×10^{-5}	n/a ^b	13
		PsA	rs4085613	1.4×10^{-3}	1.18 (1.07–1.31)	38
			rs4112788	1.1×10^{-3}	1.19 (1.07–1.32)	

Table 1 (Continued)

Gene	Chromosomal region	Ps or PsA	Genetic marker	P-value	Odds ratio (95% CI)	Reference
NFKBIA	14q13	Ps	rs8016947	1.52×10^{-11}	1.19 (1.11–1.27)	18
			rs12586317	2×10^{-8}	1.15 ^a	29
TNFAIP3	6q23	Ps	rs610604	6.54×10^{-7}	1.22 (1.13–1.32)	18
				9×10^{-12}	1.19 ^a	14
		PsA	rs610604	0.03	1.13 (1.01–1.25)	40
TNIP1	5q32–33	Ps	rs1024995	3.92×10^{-5}	1.27 (1.14–1.44)	18
			rs17728338	1×10^{-20}	1.59 ^a	14
		PsA	rs17728338	3.53×10^{-5}	1.49 (1.23–1.80)	40
TRAF3IP2	6q21	Ps	rs240993	5.29×10^{-20}	1.25 (1.16–1.34)	18
			rs458017	2.16×10^{-16}	1.37 (1.22–1.54)	
			rs33980500	1.24×10^{-16}	n/a ^b	13
			rs13210247	2.36×10^{-10}	n/a ^b	
		PsA	rs33980500	4.57×10^{-12}	1.57 (1.38–1.78)	
			rs33980500	1.13×10^{-20}	1.95 ^a	16
			rs13196377	1.39×10^{-12}	1.67 (1.45–1.93)	
			rs13190932	8.56×10^{-17}	1.83 (1.59–2.12)	
			rs13210247	1.73×10^{-14}	1.69 (1.48–1.94)	
TYK2	19p13	Ps	rs12720356	4.04×10^{-11}	1.40 (1.23–1.61)	18
			rs280519	4.42×10^{-9}	1.13 (1.05–1.21)	
ZNF313	20q13	Ps	rs2235617	1.65×10^{-6}	1.20 (1.11–1.30)	18
			rs495337	1.4×10^{-8}	1.25 (1.12–1.39)	17
				2×10^{-7}	1.21 ^a	29
		PsA	rs495337	2.5×10^{-3}	0.85 (0.76–0.94)	40

CI, confidence interval; n/a, not available; ERAP1, endoplasmic reticulum aminopeptidase 1; HLA-C, human leucocyte antigen-C; IFIH1, interferon-induced helicase C domain-containing protein 1; IL2/12B/13/21/23A/23R, interleukin-2/12B/13/21/23A/23R; IL28RA, interleukin-28 receptor, alpha subunit; LCE, late cornified envelope; NFKBIA, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; TNFAIP3, tumour necrosis factor, alpha-induced protein 3; TNIP1, TNFAIP3 interacting protein 1; TRAF3IP2, TNF receptor-associated factor 3 interacting protein 2; TYK2, tyrosine kinase 2; ZNF313 (RNF114), zinc finger protein 313. ^aCI not stated in the paper. ^bOR not stated in the paper.

there are emerging examples of genes associating with PsA but not with psoriasis which support the concept that PsA is a 'disease within a disease'. It is likely that further genetic susceptibility loci will be identified for PsA which do not confer susceptibility to psoriasis.

Despite this progress, only about 25% of psoriasis heritability has been accounted for and this is due in part to the limitations of GWAS. Firstly, there is an inability to detect alleles which make a small contribution to disease phenotype. As P-value thresholds are raised to try to eliminate false positives, alleles with small effects are lost against the background of other tested markers. The only way to solve this problem is to increase statistical power by including more cases and more controls in the study. Secondly, GWAS is based on an assumption that a common disease will be caused by common variants. This neglects rarer variants that are present in the genome which may also contribute to psoriasis susceptibility. Thirdly, GWAS currently only include SNPs in the analysis. While SNPs are the most common form of variation in the human genome, other types of variation exist such as copy number variants and insertion/deletions which could also contribute to disease. Finally, GWAS cannot measure the effect of gene–gene interaction increasing or masking their contribu-

tion to disease phenotype and epigenetic effects such as DNA methylation which influence gene expression. Indeed, the limited heritability identified to date for psoriasis is one reason why genetic findings about susceptibility cannot be immediately translated into clinical practice for population screening.

Nevertheless, there are a number of commercial companies offering genetic testing direct to the public. Many doctors do not know how to interpret the findings in the context of population risk. For example, for a disease with a lifetime prevalence of 1%, a genetic risk factor that doubles the risk (to 2%) still means there is a 98% chance of not developing disease. Secondly, the results are often based on case–control analyses, which may overestimate the risks associated with carriage of some genetic variants because they are based on hospital-based (more severe cohorts) rather than population-based series of patients. Even for diseases in which genetic loci confer a high risk of disease, such as age-related macular degeneration, there is doubt as to whether screening of the general population for genetic markers would be helpful.⁴⁶ In the case of psoriasis, the loci identified to date have improved our understanding of the aetiology of the condition but have not, as yet, led to tests with clinical utility. The area under the curve (C) from a receiver operating curve analysis is one way

Fig 1. The psoriasis/psoriatic arthritis genetic jigsaw. Genetic variants within genes involved in four broad immunological processes have been found to be associated with psoriasis and psoriatic arthritis (PsA; marked with an asterisk). There are many more pieces required to complete the psoriasis/PsA genetic jigsaw but as large-scale collaborations allied with fine mapping studies are undertaken our understanding of these complex genetic disorders will evolve significantly. NFκB, nuclear factor κB; ERAP1, endoplasmic reticulum aminopeptidase 1; HLA-C, human leucocyte antigen-C; IL2/12B/13/21/23A/23R, interleukin-2/12B/13/21/23A/23R; LCE, late cornified envelope; NFKBIA, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha; TNFAIP3, tumour necrosis factor, alpha-induced protein 3; TNIP1, TNFAIP3 interacting protein 1; TRAF3IP2, TNF receptor-associated factor 3 interacting protein 2; TYK2, tyrosine kinase 2; ZNF313, zinc finger protein 313.

of assessing the clinical validity of a model. This plots the number of correctly predicted psoriasis cases (true positives) against the number of falsely predicted cases (false positives) as the number of 'watershed' risk alleles changes. A C-value of 0.5 shows no ability to predict disease, whereas a C-value of 1 shows perfect ability to predict disease. The C-value should exceed 0.8 to be a good test. It has been estimated that, for effect sizes of 1.25–1.50 and assuming common allele frequencies, between 23 and 320 markers would be required to achieve $C > 0.8$ based on genetic markers alone. However, if there are loci with large effects on response (higher odds ratios), the discriminatory ability is higher. Alternatively, a marker or group of markers may add to the ability of clinical factors to identify responders/nonresponders and be incorporated into a predictive model.⁴⁷ It is likely that as our understanding of the genotype to phenotype correlation improves, predictions about the progression of psoriasis the condition may be possible.

Despite the fact that results from GWAS studies have not yet led to population-based screening programmes for

psoriasis, GWAS studies can have clinical usefulness in identifying pathways which can in turn be the target of novel therapies. Indeed, the 'proof of concept' for this is the biological agent, ustekinumab, which is now licensed for use in psoriasis. Ustekinumab targets the IL-23 signalling pathway, which GWAS have highlighted as being crucial to the pathogenesis of psoriasis. Hence, GWAS may facilitate the development of novel therapies. However, it is unlikely that any new therapy will be effective for all patients with psoriasis. Which patients respond optimally to which therapies may be determined, in part, by their genetic profile; indeed this is one area where genetic research may translate into improved clinical care in the short to medium term.

Pharmacogenetics of psoriasis

Translating predictors of disease to predictors of drug response

Therapies used to treat psoriasis include topical, phototherapy and systemic and biologic agents. Selection of therapy is dependent on several factors including the severity of psoriasis, response to initial therapy and patient preference. Currently, psoriasis is incurable and therapies have nonselectively targeted inflammation and epidermal hyperproliferation. However, response to such therapies is variable. Pharmacogenetics is the study of whether and how genetic variation affects patient response to drugs, and includes identification of both efficacy and toxicity predictors. Ultimately, the aim of pharmacogenetic studies is to use knowledge of the DNA sequence to identify which drug will produce the best response with the least risk of side-effects for each patient. However, it is unlikely, firstly, that a single genetic test will reliably discriminate between responders and non-responders, and, secondly, that it will be possible to identify individual gene profiles that will define who will respond well to treatment (personalized medicine) in the near future. Instead, identifying groups of patients likely to have good (or poor) responses to particular therapies, 'stratified medicine', may be more realistic and some studies have started to explore this.

For this review, only pharmacogenetic studies relating to systemic and biologic agents will be discussed. To date, all such studies in psoriasis and PsA have used a candidate gene approach where genes are selected for investigation based on knowledge of the biological pathways they lie on and the therapeutic agent to which response is being assessed. Studies using biologics have largely focused on the anti-TNF agents, while studies on systemic agents have focused on enzymes involved in drug transport and metabolism (Table 2).

Systemic agents

Methotrexate is the most researched systemic agent in the pharmacogenetics of psoriasis.^{48,49} It is often the first systemic

Table 2 Genes containing polymorphisms associated with drug response in psoriasis and psoriatic arthritis

Drug	Gene	Chromosomal region	Association	Genetic marker	P-value	Reference
Methotrexate	SLC19A1	21q22	Increased toxicity	rs1051266	0.025	53
			Drug discontinuation	rs1051266	0.048	
	TYMS	18p11	Increased toxicity	3'UTR 6 bp deletion	0.025	
			No response	5'UTR 28 bp 3 repeat	0.048	
	ATIC	2q35	Drug discontinuation	rs2372536	0.038	51
	ABCC1	16p13	Response	rs35592	8×10^{-3}	
				rs28364006	0.02	
				rs2238476	0.02	
				rs2238476	0.01	
			Adverse events	rs3784864	0.03	
				rs246240	6×10^{-4}	
				rs3784862	2×10^{-3}	
				rs1967120	0.01	
	ABCG2	4q22	Response	rs11075291	8×10^{-3}	
				rs13120400	0.03	
				rs17731538	7×10^{-3}	
				rs5760410	0.03	
				rs1051266	0.03	
Acitretin	ADORA2A	22q11	Response	rs1232027	0.02	56
	SLC19A1	21q22	Response	rs1801133	0.04	
	DHFR	5q11	Response	rs833061 T/T	0.04	59
	MTHFR	1p36	Increased toxicity	rs833061 T/C	0.01	
	VEGF	6p12	No response	rs1799724	0.03	61
Adalimumab	TNF	6p21	Response	rs1799964	0.04	
	TNF	6p21	Response			

SLC19A1, solute carrier family 19 (folate transporter), member 1; TYMS, thymidylate synthetase; ATIC, 5-aminoimidazole-4-carboxamide ribonucleotide transformylase; ABCC1, ATP-binding cassette, subfamily C (CFTR/MRP), member 1; ABCG2, ATP-binding cassette, subfamily G (WHITE), member 2; ADORA2A, adenosine A2a receptor; DHFR, dihydrofolate reductase; MTHFR, methylenetetrahydrofolate reductase; VEGF, vascular endothelial growth factor; TNF, tumour necrosis factor; UTR, untranslated region.

therapy used to treat moderate to severe psoriasis but has variable interindividual responses, and approximately 30% of treated individuals develop side-effects, including hepatotoxicity and gastrointestinal toxicity.⁵⁰ Methotrexate requires intracellular uptake and inhibits enzymes of the folate, purine and pyrimidine pathways, although the mechanism by which the drug exerts its effects in psoriasis and PsA are poorly understood. Nonetheless, the focus of many pharmacogenetic studies on methotrexate has been on the genes involved in its uptake and subsequent metabolism (Table 2). The largest of these studies reported a significant association between SNPs within the genes regulating the intracellular uptake of methotrexate, ABCC1 and ABCG2, and improved drug response.⁵¹ The ABC genes are transporter genes of the ATP-binding cassette family. Five SNPs in ABCC1 were also found to be significantly associated with increased toxicity to methotrexate. In the same cohort, no associations with treatment response were found in genes coding for enzymes involved in methotrexate metabolism; folypolyglutamate synthase (FPGS), gamma-glutamyl hydrolase (GGH), methylenetetrahydrofolate reductase (MTHFR) and 5-aminoimidazole-4-carboxamide ribonucleotide transformylase (ATIC).⁵² Methotrexate toxicity has also been associated with a variant in the reduced folate carrier 1 gene (RFC1) gene, which is involved in regulating folate levels.⁵³

Several studies have investigated genetic variation in the thymidylate synthase (TYMS) gene, which is involved in the production of thymidine triphosphate (TTP) required for DNA synthesis. Different variants have been investigated with conflicting results.^{53–55}

The only pharmacogenetic study to be carried out exclusively in patients with PsA to date identified a polymorphism in the dihydrofolate reductase gene (DHFR) that was associated with better response to methotrexate.⁵⁶ DHFR converts dihydrofolate to tetrahydrofolate, which is required for DNA synthesis and cell growth. Although this enzyme is inhibited by methotrexate it is not clear if this inhibition is crucial to its anti-inflammatory effects. The study identified another gene, MTHFR, which contained a SNP associated with increased hepatotoxicity. MTHFR is crucial for thymidine synthesis, necessary for cellular proliferation, and it is interesting to note the same SNP has been associated with a higher risk of developing adverse effects in patients with rheumatoid arthritis treated with methotrexate.⁵⁷

Ciclosporin and acitretin are the two other major systemic drugs used to treat psoriasis. While no pharmacogenetic studies have yet been reported with ciclosporin, two have been performed with acitretin. The first of these examined polymorphisms in the apolipoprotein E gene (APOE) but found no

association with response.⁵⁸ The second reported that a variant at position -460 of the vascular endothelial growth factor (VEGF) gene was significantly associated with resistance to treatment with acitretin in psoriasis.⁵⁹ These findings require replication for validity.

Biologic agents

Biologic agents are products that have been isolated from living organisms rather than synthesized by chemical methods. They are used to treat psoriasis and/or PsA in the setting of a contraindication and/or lack of efficacy of two or more systemic agents and phototherapy. Unlike systemic agents, they target specific biological pathways. Currently, there are five biologics used to treat psoriasis. Adalimumab (Humira®; Abbott Laboratories Ltd, Maidenhead, U.K.), etanercept (Enbrel®; Wyeth Pharmaceuticals, Maidenhead, U.K.) and infliximab (Remicade®; Schering-Plough, Welwyn Garden City, U.K.) target the TNF- α pathway, important in the inflammatory process of several diseases including psoriasis.⁶⁰ Ustekinumab (Stelara®; Janssen-Cilag, High Wycombe, U.K.) targets IL-12 and IL-23, both of which have been implicated extensively in GWAS of psoriasis susceptibility, and alefacept (Amevive®; Astellas Pharma Ltd, Wallisellen, Switzerland) targets T cells, but Switzerland is the only European country where it is licensed for use along with North America and Australia.

Two studies have reported genetic associations with response to anti-TNF therapy in psoriasis (Table 2). The first reported an association with a SNP in the TNF gene promoter region at position -1031 (rs1799964)⁶¹ in a small sample cohort. The outcome measure used to assess response was based on patient-rated response and may have been subject to bias.⁶¹ Hence, replication studies are required to confirm those findings. The second study combined patients with rheumatoid arthritis and ankylosing spondylitis and patients with PsA to analyse the effect of a TNF promoter region SNP at -308 (rs1800629)⁶² on response to three anti-TNF drugs. The study found significant association with increased response, but only 10 patients with PsA were included. Nonetheless, it is interesting to note that a meta-analysis of similar studies of this polymorphism in patients with rheumatoid arthritis treated with anti-TNF biologics has shown that it is significantly associated with response to etanercept and infliximab, respectively.⁶³ Two other studies investigated the role of HLA-C, in determining response to biologics, but found no association.^{64,65}

Limitations and future work

The pharmacogenetic studies undertaken to date have a number of limitations. Firstly, they often suffer from lack of power to detect association due to low sample size; typically studies have involved fewer than 100 patients.^{61,62} By contrast, GWAS of psoriasis susceptibility usually involve over 1000 patients and similarly sized control groups. Secondly, no independent replication is reported so the likelihood is that some of the

associations will be false-positive findings. The ability to detect and replicate associations is hampered by the lack of agreed criteria for measuring drug response. For example, the Psoriasis Area and Severity Index (PASI)⁶⁶ is often used to assess the clinical severity of psoriasis, but different percentage reductions in PASI, e.g. 90%, 75% and 50% have been used to define significant, clinically relevant improvement. Other limitations include the study of a single variant within a candidate gene with no attempt to investigate systematically an association with variants spanning the gene. Furthermore, factors such as alcohol intake and stress can be associated with non-response and studies often do not account for these possible confounders.^{67,68} Finally, the studies have largely selected candidate genes based on knowledge of the pathways involved in drug metabolism or signalling. However, a recent study in rheumatoid arthritis reported a disease susceptibility locus, protein tyrosine phosphatase, receptor type C (PTPRC), which appears to be predictive of patient response to TNF- α blockade.⁶⁹ This has highlighted the possibility that disease susceptibility genes may also predict biologic drug response in psoriasis. Indeed, several psoriasis susceptibility genes encode proteins that lie on the pathways targeted by available therapies. For example, the IL12B, IL23R and IL23A genes are all involved in the IL-17-signalling pathway targeted by ustekinumab, while the TRAF3IP2 and TNFAIP3 gene products are involved in the TNF- α -signalling pathway which is a target of biologics including etanercept, adalimumab and infliximab. Pharmacogenetic studies in psoriasis, to date, however, have mainly investigated genes that have not been identified as conferring psoriasis susceptibility.

Conclusion

To date, 15 genes are associated with psoriasis, 11 genes are associated with PsA and 10 genes are associated with both, including HLA-C, IL12B, IL23R and TRAF3IP2. Variation within the IL13 gene locus and the HLA-B27 allele has been associated with PsA but not with psoriasis in most of the studies undertaken. While the debate as to whether all psoriasis susceptibility genes are also PsA genes is still in question, the fact that the HLA-Cw6 allele is significantly more associated with psoriasis compared with PsA suggests there may be some differences. Further study is needed to establish whether there is complete commonality of inflammatory pathways in both diseases. Future work in understanding which pathways are essential in which patient types may enable more therapies to be developed for these diseases.

It is clear that the pharmacogenetics of both psoriasis and PsA is very much in its infancy. Few studies have been undertaken in either disease and those that have are limited in both study design and size. The most researched drug thus far, methotrexate, appears to have plausible markers which may predict treatment response but all require validation. It is likely that one of the keys to stratified medicine in psoriasis will be identification of disease susceptibility genes which may also be predictors of treatment response.

What's already known about this topic?

- Psoriasis and psoriatic arthritis are complex diseases with both genetic susceptibility and environmental triggers contributing to onset.
- Genome-wide association studies (GWAS) have advanced our knowledge of the genetics of both diseases.
- Psoriasis and psoriatic arthritis share a number of susceptibility loci.
- Patients show interindividual variation in their response to biologic and systemic drugs.

What does this study add?

- A summary of psoriasis susceptibility loci and pathways identified by GWAS and contrasted with those pertaining to psoriatic arthritis.
- Awareness that disease susceptibility alleles may also be predictors of drug response.
- Acknowledgment that pharmacogenetic studies in psoriasis and psoriatic arthritis are both few in number and weak, thereby identifying an area where further research is required.

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