

The Long and Winding Road: Searching for Non-MHC Psoriasis Susceptibility Loci

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Abstract: It is well recognised that the Major Histocompatibility Complex (MHC) harbours the main psoriasis susceptibility locus (PSORS1, Psoriasis Susceptibility 1). Nonetheless, linkage analyses have repeatedly shown that the PSORS1 locus account for less than 50% of the disease family clustering. On this basis, it is widely agreed that additional loci must contribute to psoriasis susceptibility, either by interacting directly with or by modifying the effect of the PSORS1 gene(s). To date, at least eight putative disease susceptibility regions have been mapped outside of the MHC (PSORS2-9). However, the search for the underlying genetic determinants has been seriously hindered by the difficulty of replicating linkage to these loci. The small disease-risk conferred by non-MHC genes and the likely occurrence of genetic heterogeneity are regarded as the main factors affecting the power of linkage studies and confounding the interpretation of experimental results. Evidence supporting some non-MHC loci has been provided by their close overlap with genomic regions conferring susceptibility to other inflammatory disorders. These observations indicate that clinically distinct autoimmune diseases might share common pathogenic pathways, suggesting that future advances in the understanding of single disorders could benefit the wider research community studying common inflammatory diseases.

Key Words: Psoriasis susceptibility, non-MHC loci.

INTRODUCTION

Psoriasis susceptibility is regarded as a complex trait, resulting from the combined action of multiple genes [1, 2]. Genome-wide scans and association studies carried out in a wide range of populations have clearly demonstrated that the primary susceptibility locus (PSORS1) lies on chromosome 6p21, within the Major Histocompatibility Complex (MHC) region (see Elder *et al.*, in this issue). Conversely it has become apparent that the PSORS1 locus accounts for less than 50% of psoriasis familial clustering [3] and that PSORS1 risk haplotypes are found in up to 37% of control chromosomes [4]. The MHC region being neither necessary nor sufficient to trigger the onset of psoriasis, additional genetic factors are likely to be required. Complex segregation analyses have repeatedly indicated that the pattern of disease transmission observed in psoriasis pedigrees is best accounted for by a multifactorial inheritance model [2, 5, 6]. Based on these observations, several research groups have focused their efforts on the search of psoriasis susceptibility loci lying outside of the MHC. This has proven an extremely difficult endeavour, owing to the small biological effect of individual non-MHC susceptibility genes. Nonetheless, a decade of significant efforts from the research community has allowed the characterisation of a small number of candidate regions. Here, we review the progress of this laborious enterprise and consider the main obstacles still lying ahead.

THE CURRENT STATE OF RESEARCH

Genome-wide scans have mapped no less than eight psoriasis susceptibility loci outside of the MHC (regions PSORS2-9 in Table 1). A number of additional loci, supported by weaker statistical evidence have also been proposed (undesignated regions in Table 1). Only a fraction of the published locations have been validated in independent cohorts, with a single one (PSORS2) showing evidence for linkage in more than two follow-up studies (Table 1). However, it is of interest that at least five PSORS intervals overlap with loci conferring susceptibility to other inflammatory disorders (Table 2).

The refinement of several PSORS loci has also been undertaken, using linkage disequilibrium (LD) fine mapping. This approach relies on the assumption that the marker alleles lying in close proximity to a susceptibility mutation are likely to be co-inherited with it and to demonstrate disease association, as a consequence. Thus, the analysis of dense microsatellite maps spanning linkage intervals is expected to identify markers bearing disease associated alleles and highlighting the most likely location of the susceptibility gene [7]. It is also worth noting that the observation of allelic association within linkage intervals provides further evidence supporting their original assignment.

Thus far, LD based fine mapping has allowed the refinement of the PSORS2, PSORS4 and PSORS5 susceptibility loci (Table 3).

High-resolution genetic analysis of the refined PSORS2 interval has recently identified a putative susceptibility allele, mapping between the SLC9AR1 and NAT9 genes and abolishing a site for the RUNX1 transcription factor [8]. The

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Table 1. Published Non-MHC Loci

Chromosome (locus name)	First report	Validation
1p (PSORS7)	UK, 2001 [26]	
1q (PSORS4)	Italy, 1999 [27]	US, 2001 [28]
2p	US, 1998 [29]	UK, 2001 [26]
2q	UK, 1997 [30]	
3q (PSORS5)	Sweden, 1999 [31]	
4q13	US, 1998 [29]	Sweden, 1999 [31]
4q31 (PSORS9)	China, 2003 [32]	
4q34 (PSORS3)	Ireland, 1996 [33]	
6q	US/Germany, 1997 [34]	
7	UK, 2001 [26]	
8q	UK, 1997 [30]	
10q	US/Germany, 1997 [34]	
14q	US, 1998 [29]	UK, 2001 [26]
15	Sweden, 1999 [31]	
16q (PSORS8)	US/Germany, 1997 [34]	* Iceland, 2003 [35]
17q25 (PSORS2)	US, 1994 [36]	US/Germany, 1997 [34]; Sweden, 1999 [37]; China, 2003 [38].
18p	UK, 2001 [26]	Finland, 2003 [39]
19p13 (PSORS6)	Germany, 2000 [40]	UK, 2001 [26]
20p	UK, 1997 [30]	US/Germany, 1997 [34]

* psoriatic arthritis cohort

same authors were able to detect a distinct cluster of SNPs, lying in intron 3 of the RAPTOR gene and displaying independent evidence for association with psoriasis [8]. Our group has been able to replicate the association with RAPTOR SNPs but not that with SLC9AR1/NAT9 variants (Capon *et al.*, 2004 [42]). Altogether, these observations suggest that two distinct susceptibility genes underlie the PSORS2 interval that was originally defined by linkage analysis.

Table 2. Inflammatory Disease Loci Overlapping with PSORS Intervals

Locus	Disease	PSORS region
ATOD4	Atopic dermatitis [21]	PSORS2
ATOD2	Atopic dermatitis [21]	PSORS4
ATOD1	Atopic dermatitis [21]	PSORS5
IBD6	Inflammatory bowel disease [40]	PSORS6
IBD1	Crohn's disease [34]	PSORS8

The PSORS4 locus might also contain multiple risk alleles, as the critical region encompasses part of the Epidermal Differentiation Complex [9], a cluster of more than

40 genes involved in the processes of keratinocyte terminal differentiation [10]. However, the analysis of PSORS4 positional candidates has yet to identify nucleotide variants that are significantly associated with psoriasis (Table 3).

Table 3. Refinement of Linkage Intervals

Locus	Minimal interval	Positional candidate
PSORS2	20 kb [8]	SLC9AR1/NAT9 [8] RAPTOR [8]
PSORS4	100 kb [9]	S100A7, excluded [41] LOR
PSORS5	160 kb [11]	SLC12A8 [11]

Genetic analysis of the PSORS5 interval has identified disease associated SNPs within the SLC12A8 gene [11]. However, the clustering of these substitutions in non-coding regions and the poorly characterised function of the protein suggest caution in the interpretation of these findings.

WHY IS IT TAKING SO LONG?

The perseverance of the research community investigating non-MHC susceptibility loci has undoubtedly generated several significant results. Despite these advances, a number

of fundamental questions still need to be addressed. We ignore how many non-MHC loci are actually contributing to psoriasis susceptibility. We do not know whether these loci are genetically heterogeneous among different population or within a same ethnic group. We are unable to establish whether non-MHC loci are epistatically interacting with PSORS1 and/or with each other. Such uncertainties plague the study of most complex traits and typically arise from the difficulty of comparing results from independent studies. While a failure to replicate linkage for a monogenic condition demonstrates the existence of additional disease loci, the same unequivocal conclusion cannot be reached when the same finding applies to a multifactorial trait. A host of confounding factors have to be taken into account, when interpreting negative results from the genetic analysis of a complex trait. Simulation studies have demonstrated that even LOD scores obtained from repeat sampling of a same population show a pronounced variability [12]. Thus, replication of a given locus at the same significance level will require a sample that exceeds the original by several times [12, 13]. Cohorts obtained from a different ethnic group may need to be even larger, the population frequency of individual susceptibility alleles strongly influencing the sensitivity of linkage detection [12, 13]. Conversely, the recruitment of extended patient cohorts is liable to increase the degree of clinical heterogeneity present within the sample. Notably, a collaborative analysis of 942 sib-pairs recruited in three different centres has failed to replicate linkage to the PSORS2, PSORS4 or PSORS5 loci [3]. Likewise, our analysis of PSORS2 SNPs could provide evidence of disease association only in a subset of patients presenting with a well-documented family history of psoriasis (Capon *et al.*, 2004 [42]). The notion that clinical heterogeneity may confuse genetic studies is also supported by the observation that various psoriasis subtypes show differential association with PSORS1 alleles [14].

Experimental design is another well-recognised confounder of complex disease genetic analysis. The eleven

genome scans published to date have been analysed using a variety of statistical methods, each likely to display differential power to detect linkage [15]. Moreover, some studies have been carried out in a single phase, whereas others have adopted a two-stage approach (Table 4). When this latter strategy is selected, putative susceptibility regions are identified in a preliminary round of genotyping and later validated by the analysis of a larger sample or a denser marker map. Although the rationale for two-stage genome scans is well documented [16], the use of diverse experimental designs clearly complicates the comparison of results that have been obtained in different studies.

FUTURE DIRECTIONS

Identifying disease susceptibility genes conferring a modest relative risk is clearly a challenging task. Nonetheless, the literature in this field is visibly expanding and the last few months have witnessed the characterisation of genes contributing to the pathogenesis of asthma [17], rheumatoid arthritis [18] and ischemic stroke [19]. Likewise, the characterisation of putative PSORS2 susceptibility alleles [8] confirms that the positional cloning of psoriasis susceptibility genes is a realistically achievable task, albeit a lengthy and arduous one. The identification of PSORS2 risk alleles will also allow researchers to directly assess the relevance of these variants in diverse populations, by means of association studies. This latter approach offers greater statistical power to detect loci of small effect, compared to linkage analyses [20]. Indeed, our group was able to detect association with PSORS2 SNPs in a dataset that did not demonstrate any linkage to this genomic region (Capon *et al.*, submitted for publication). Because of the overlap between PSORS2 and the atopic dermatitis (AD) susceptibility locus ATOD4 [21], the molecular characterisation of this region [8] could also benefit the understanding of a distinct skin disorder. The reverse process may also occur, with genes identified in atopic dermatitis cohorts being analysed as candidates for psoriasis susceptibility. The identification of

Table 4. Experimental Approaches Adopted in Psoriasis Genome Scans

Authors	Study design	Notes
Thomfohrde <i>et al.</i> [36]	Two-stage	A susceptibility locus identified by genome-wide scan of a large family was validated in further pedigrees
Matthews <i>et al.</i> [33]	Two-stage	A susceptibility locus identified by genome-wide scan of a large family was validated in further pedigrees
Trembath <i>et al.</i> [30]	Two-stage	Susceptibility loci identified by genome scan were validated by analysis of a denser marker map
Nair <i>et al.</i> [34]	One stage	
Capon <i>et al.</i> [27]	Two-stage	A susceptibility locus identified by genome-wide scan of a large family was validated in further pedigrees
Enlund <i>et al.</i> [31]	Two-stage	A susceptibility locus identified by genome-wide scan of a 20 families was validated in further pedigrees
Lee <i>et al.</i> [40]	One stage	
Veal <i>et al.</i> [26]	One stage	
Karason <i>et al.</i> [35]	One stage	Families were ascertained through probands affected by psoriatic arthritis
Zheng <i>et al.</i> [32]	One stage	
Asumalahti <i>et al.</i> [39]	Two-stage	The genome scan was restricted to families that did not show linkage to PSORS1 markers

CTLA4 SNPs conferring risk to both Graves' disease, autoimmune hypothyroidism and type 1 diabetes demonstrates the power of this approach, whilst indicating the existence of immune system regulatory genes whose alteration can predispose to a range of clinically distinct autoimmune phenotypes [22]. The observation that the regulatory SNPs predisposing to systemic lupus erythematosus, psoriasis and rheumatoid arthritis all affect the binding of the same transcription factor (i.e. RUNX1, a protein involved in haematopoietic development and T-cell differentiation) is also leading support to the hypothesis of inflammatory pathways shared by diverse disorders [23].

CONCLUSIONS

The last few years have witnessed significant advances in the understanding of autoimmune diseases, showing that the persistence of geneticists studying these conditions is likely to be rewarded by the discovery of novel regulatory pathways and potential therapeutic targets. The low penetrance of non-MHC psoriasis susceptibility genes remains a major impediment in these studies, as it greatly affects the power that can be achieved by genetic analysis. Conversely, the establishment of multi-centre collaborations has become a frequent practice within the psoriasis research community (see [3, 24]). The increasing availability of reliable technologies for automated genotyping currently allows a high-resolution analysis of the extended patient resources recruited by such consortia. This kind of collaborative approach has proved fruitful in the past [4, 25] and now holds the promise to address some of the long standing questions in psoriasis genetics.

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ABBREVIATIONS

PSORS locus = Psoriasis Susceptibility locus
 MHC = Major Histocompatibility Complex
 LD = linkage disequilibrium

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