

Molecular genetics of Psoriasis

(Principles, technology, gene location, genetic polymorphism and gene expression)

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Summary: Psoriasis is a common inflammatory skin disease with an etiology based on both environmental and genetic factors. As is the case of many autoimmune diseases its real cause remains poorly defined. However, it is known that genetic factors contribute to disease susceptibility. The linkage analysis has been used to identify multiple loci and alleles that confer risk of the disease. Some other studies have focused upon single nucleotide polymorphisms (SNPs) for mapping of probable causal variants. Other studies, using genome-wide analytical techniques, tried to link the disease to copy number variants (CNVs) that are segments of DNA ranging in size from kilobases to megabases that vary in copy number. CNVs represent an important element of genomic polymorphism in humans and harboring dosage-sensitive genes may cause or predispose to a variety of human genetic diseases. The mechanisms giving rise to SNPs and CNVs can be considered as fundamental processes underlying gene duplications, deletions, insertions, inversions and complex combinations of rearrangements. The duplicated genes being the results of 'successful' copies are fixed and maintained in the population. Conversely, many 'unsuccessful' duplicates remain in the genome as pseudogenes. There is another form of genetic variations termed copy-neutral loss of heterozygosity (LOH) with less information about their potential impact on complex diseases. Additional studies would include associated gene expression variations with either SNPs or CNVs. Now many genetic techniques such as PCR, real time PCR, microarray and restriction fragment length analysis are available for detecting genetic polymorphisms, gene mapping and estimation of gene expression. Recently, the scientists have used these tools to define genetic signatures of disease, to understand genetic causes of disease and to characterize the effects of certain drugs on gene expression. This review highlights the principles, technology and applications on psoriasis.

Key words: Psoriasis, Genes, and Cytokine.

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INTRODUCTION

Psoriasis is a common inflammatory skin disease with an etiology based on both environmental and genetic factors. As is the case of many autoimmune diseases its real cause remains poorly defined. However, it is known that genetic factors contribute to disease susceptibility. The linkage analysis has been used to identify multiple loci and alleles that confer risk of the disease. Some other studies have focused upon single nucleotide polymorphisms (SNPs) for mapping of probable causal variants. Other studies, using genome-wide analytical techniques, tried to link the disease to copy number variants (CNVs) that are segments of DNA ranging in size from kilobases to megabases that vary in copy number. The mechanisms giving rise to SNPs and CNVs can be considered as fundamental processes underlying gene duplications, deletions, insertions, inversions and complex combinations of rearrangements. There is another form of genetic variations termed copy-neutral loss of heterozygosity (LOH) with less information about their potential impact on complex diseases. Now many genetic techniques such as PCR, real time PCR, microarray and restriction fragment length analysis are available for detecting genetic polymorphisms, gene mapping and estimation of gene expression. This review highlights the principles, technology and applications on psoriasis.

Human genetic variations

Rapid advancements in human genetic studies have led investigators to use the recent research methods, including linkage analysis and association-based fine mapping of haplotypes harboring disease-susceptibility alleles with single-nucleotide polymorphism (SNP) analysis. (1) Genetic variations within

the human genome can take other forms, including copy number variations (CNVs), and copy-neutral loss of heterozygosity (LOH). Therefore, several kinds of human genetic polymorphism databases became available in exploring genetic information for various applications. With only a preliminary understanding of the roles CNVs and LOH play in complex disease development. (2) However, SNPs involve the change in a single nucleotide, while CNVs and LOH encompass larger segments of DNA. In a recent study, SNP genotypes and CNV measurements were associated with 83% and 18% of those gene expression traits for which statistically significant associations were found. (3) This may still underestimate the role of CNVs, given the greater completeness and accuracy with which SNPs can be queried at present. Initially, this review, focus only on understanding the principles of SNPs and CNVs with the methods for detection these structural variations and their potential involvement in disease manifestations. While, LOH have not been included in this review because of the less information currently available regarding their effects; although, their potential impact on complex diseases is enormous.

I-Single nucleotide polymorphism (SNP):

Among the many important insights derived from completion of the Human Genome Project was the recognition of the abundance of single nucleotide polymorphisms (SNPs) as a major source of genetic variation, leading to speculation that the bulk of phenotypic variability in human populations. SNPs have been shown to be responsible for differences in susceptibility to disease and response to drug therapies. The specificity of SNPs is likely to be compromised with most of the current PCR based methods used to genotype a target locus

in the presence of a highly homologous duplicated region. Such a lack of locus specificity could inflate the heterozygosity of the SNPs. SNPs have become a key tool in investigating how genes interplay in complex diseases. Based on the common disease – common variant (CD-CV) hypothesis, alleles with high heterozygosity are normally preferred. However, in duplicated regions of the genome with a high level of homology, a lack of locus specificity of the amplicon used to genotype nucleotide variants could inflate the density of SNPs. (4) That is, the nucleotides that are present in equivalent locations of the duplicated regions, but vary between the two loci, would appear to have a heterozygous genotype by inadvertent co-amplification of the duplicated region (s). This single base variation in the equivalent position of the duplicon is known as a paralogous sequence variant (PSV), or cismorphism, and the presence of such a PSV would always yield a heterozygous reading when genotyped. Also, if the nucleotide at an equivalent position of a duplicon is same as that of the actual genomic region, one must take appropriate measures to determine whether the polymorphism resides in the gene or a duplicated region. Observations would be even further complicated if the base is polymorphic at more than one site, as in case of multi-site variants (MSVs). It is likely that any of the above cases could be misread as SNPs, and thereby elevate the ostensible heterozygosity of the probing base of the target gene. (5) As a result, intense efforts were made to develop high-throughput sequencing and SNP genotyping platforms, SNP databases, detailed linkage disequilibrium maps (through the International HapMap Project11), and statistical methodologies for analyzing SNP genotype and haplotype data in mapping disease-susceptibility genes. Until recently, the overwhelming majority of gene-mapping studies have focused exclusively on the role

of SNPs in human diseases. Indeed, using population-based studies to identify genetic determinants of common disease, dozens of SNP-based susceptibility variants have been identified for human diseases. (6-7) However, SNP databases developed through a series of phases: first, rapid growth in methods to detect the locations of putative SNPs; second, calibration and standardization of discovery methods to maximize sensitivity and minimize false positives; (8) third, accurate genotyping of large numbers of SNPs to validate (or invalidate) SNPs and characterize their properties; (9-10) and fourth, assessment of the sensitivity of the resulting map in comparison to systematic resequencing data. (11).

I-A. Mapping psoriasis-susceptibility loci:

By using genome-wide scans, investigators have mapped (with varying degrees of confidence) at least six different susceptibility loci, designated PSORS1–PSORS6. (1) Several other psoriasis-susceptibility loci have been mapped, including PSORS7 (1p) and PSORS9 (4q31), and additional studies are ongoing in many laboratories. (12-13-14) The major genetic determinant for psoriasis is within the PSORS1 region of the MHC on chromosome 6p21, as reported by several independent groups, accounting for 30–50% genetic susceptibility (Table 1.) (1)

However, the major histocompatibility complex (MHC) region is an extraordinarily gene dense area which encodes at least 250 genes. It is divided into three classes: classes I, II and III. The class I and class II regions encode the classical antigen-presenting molecules HLA-(A1, A2, B13, B17, B37, B39, B57, Cw6, Cw7, DR4, DR7, DR10, DR55, DR57, DQ9 , Alanine-73) ; (15) and class III encodes genes of which some are of

immunological interest (e.g. complement factors, tumour necrosis factor (TNF), heat shock protein 70 (HSp70) reviewed by Schaschl et al. (16) Since 30 years, the linkage analysis has been used to identify multiple loci and alleles that confer risk of the disease. The two most likely candidate loci at 6p21.3 are HLA-Cw*0602 and the corneodesmosin (CDSN) gene, which encodes an adhesive protein expressed by keratinocytes and is important in terminal differentiation of the epidermis, although interpretation is complicated by the extraordinary linkage disequilibrium observed around the MHC. Thus, it is possible that genes such as HLA-Cw6 are in linkage disequilibrium with another gene, or block of genes, at a distinct locus such as killer Ig-like receptor (KIR), as recently reported by Martin et al., 2002. (17) KIRs may be important in psoriasis (and psoriatic arthritis), since they are expressed in lesional skin and have thus given rise to the consideration of innate immunity in psoriatic lesions. (18) Whereas the similarity of the HLA associations obtained in different pedigree according to age of patients or different ethnic population (about 10% of HLA-Cw6-positive individuals). (19) Why is this? The environmental factors such as streptococcal infection and stress undoubtedly play a role. Elder et al. (20) believed that this is primarily because of a requirement or additional disease alleles, encoded by different genes in the same person. Presumably, these genetic and environmental factors are not present in the right combination up to 90% of the time. Henseler and Christophers, (21) defined type I psoriasis as having age of onset younger than 40 years, with strong HLA associations. Patients with type II disease were characterized by age of onset 40 years or older, and much weaker HLA association. (22) In northern Europe and United States, only about two thirds of psoriatic patients carry HLA-Cw6 (and therefore carry

PSORS1). A recent study from England found that 100% of 29 patients with poststreptococcal guttate psoriasis were positive for HLA-Cw6. (23) This finding suggests that the PSORS1 gene plays a major role in this form of psoriasis. This finding fits with the predominance of PSORS1 in juvenile-onset psoriasis, together with the fact that poststreptococcal guttate psoriasis is typically observed in younger individuals. In many of these individuals, disease resolves completely, without the evolution of chronic plaque disease. This is even lower in most oriental populations, where many affected individuals carry HLA-Cw7. Also, strong associations with HLA-B57 were found. In an effort to explain this observation, others have postulated a primary role for alanine at position 73 of the HLA-C protein molecule, which is also found on HLA-Cw7.

The second most well-characterized disease-susceptibility locus (PSORS2) resides within 17q24-q25. Linkage of psoriasis to this locus has been identified by independent family sets. (24-25) Two candidate genes in this region are SLC9A3R1 and NAT9. (26) A susceptibility locus for psoriasis, PSORS4, has been mapped to chromosome 1q21 in the region of the epidermal differentiation complex. Therefore, Kainu et al., (27) have analysed association to three candidate gene clusters of the region, the S100, small proline-rich protein (SPRR) and PGLYRP (peptidoglycan recognition protein) genes, which all contain functionally interesting psoriasis candidate genes. Chen et al., (28) added two more genes, involucrin (IVL) and praline-rich region9 (PRR9) in their studies on Singaporean Chinese psoriatic patients. Nair et al., (29) provided strong support for the association of at least seven genetic loci in European psoriasis cases. Loci with confirmed association include HLA-C, three genes involved in IL-23 signaling (IL23A, IL23R, IL12B), two genes that act downstream of

TNF-alpha and regulate NF-kappa B signaling (TNIP1, TNFAIP3) and two genes involved in the modulation of Th2 immune responses (IL4, IL13). In psoriasis Chinese patients Zhang et al., (30) identified a new susceptibility locus within the LCE gene cluster on 1q21.

I-B. Psoriasis gene polymorphisms:

During the past decade, numerous reports have provided additional molecular details concerning genetic polymorphism of psoriasis including cytokine, cytokine receptors, chemokines, chemokines receptors growth factors, signal transduction pathways, transcription factors, and other factors. Some of the most prominent components are listed in numerous reports (Table 2).

Cytokines: Recent large-scale genome-wide association studies have yielded new candidates in genes encoding cytokines with functional relevance to psoriasis. Polymorphisms within the genes encoding the IL-12 p40 subunit, IL12B, and one of the IL-23 receptor subunits, IL23R, have been replicated in US and European populations and overlap with risk of Crohn's disease (Reference). Polymorphisms within the gene encoding IL-13, a Th2 cytokine, also confer risk for psoriasis (Reference). Variants of the gene IL15 encoding IL-15 have been identified that associate with psoriasis in a Chinese population (Reference). These discoveries pose the challenge of elucidating the role of common genetic variants in susceptibility to and manifestations of psoriasis. Pietrzak et al. and Duffin and Krueger (31, 32) listed the following cytokines which are directly involved in psoriasis: TNF, IL-1, IL-2, IL-6, IL-7, IL-8, IL-15, IL-18, IL-19, IL-20, IL-23, IL-4, IL-10, and IL-12 as well as IL-11, IL-17, and IFN-gamma which are rather indirectly engaged. (Table 3).

II. Copy Number Variations

The known role of copy-number alterations in sporadic genomic disorders, combined with emerging information about inherited copy number variation, indicate the importance of systematically assessing copy-number variants (CNVs), including common copy-number polymorphisms (CNPs), in disease investigation.(33) However, CNVs are new tools defined as additions or deletions in the number of copies of a particular segment of DNA (larger than 1kb in length) when compared to a reference genome sequence. They provide further insight into the complexity and diversity of genetic variations. CNVs influence the transcriptional or translational levels of overlapping or nearby genes, gene expression, phenotypic variation, and adaptation by altering gene dosage. (34-35) CNVs can therefore cause a disease, or contribute to risks of various complex trait diseases among individuals. Whenever possible, initial reports of CNV-disease association should include independent evidence of replication in other studies and populations. Generating such data may frequently include sharing of DNA samples given the current technical challenges of CNV genotyping and operator-dependence of quantitative genotyping assays like qPCR.(36) Recent developments and applications of genome-wide structural-variation technologies have led to the identification of thousands of heritable CNVs covering ~360 Mb, or ~12% of the nucleotide sequence in the human genome (5) and sparked considerable interest.(37-38) Currently, 5,672 CNV loci are catalogued in the Database of Genomic Variants. Indeed, a number of recent studies have demonstrated an association between a polymorphism and human diseases including immunity, and inflammation. Although case-control studies require reliable large-scale genotyping, but accurate measurement of CNV has proven to be technically challenging.(39) Chee-Seng et al.(2) have

begun exploring the extent of CNVs in several South-East Asian populations (Singaporean Chinese, Malay, and Indian) with the goal of constructing a genome-wide map reflecting CNVs and copy-neutral LOH within these populations. Their studies, demonstrate the advantages of using high-density SNP arrays for this purpose. Technical challenges in CNV studies and CNV-based association studies pose additional unique challenges, including choice of genotyping platform and DNA quality control.(40) Three broad platform classes are currently available for genome-wide copy-number surveys: [1] large insert clone-based comparative genomic hybridization; [2] long, isothermic oligonucleotide-based CGH arrays and [3] SNP-based arrays. (41,42,43) Statistical challenges in analysis of CNV associations with human disease are also a problem. Genetic epidemiology of CNVs is still in its infancy— so too are the statistical methods for the analysis of CNV association with disease. Some previous studies have developed Paralogue Ratio Tests (PRT) determination at many genes copy number variant.

Initially, CNV was applied on beta-defensins which are small, secreted, antimicrobial peptides, and encoded by DEFB genes in three main gene clusters: two on chromosome 20 and one on 8p23.11. The central role of these proteins in the innate immune system of the skin suggested that beta-defensin genes could be candidate genes for psoriasis susceptibility. Of the eight beta-defensin proteins, hBD-2, hBD-3 and hBD-4 (encoded by DEFB4, DEFB103 and DEFB104 gene at 8p23.1 respectively) have been found to stimulate keratinocytes to release IL-8, IL-18 and IL-20, which are all proinflammatory cytokines that have an established role in the etiology of psoriasis. Seven out of eight genes including, DEFB4, SPAG11, DEFB103, DEFB104, DEFB105, DEFB106 and DEFB107 are on a large repeat

unit that is variable in copy number. (35) Individuals have between 2 and 12 copies per diploid genome, with a modal copy number of four in UK. Hollox et al. (44), found an association between higher CNVs for DEFB on chromosome 8p23.1 and risk of psoriatic German patients. As an alternative assay for beta-defensin copy number, they used the higher-throughput Paralogue Ratio Test (PRT) which has been successfully employed in a case-control study to identify an association between DEFB4 copy number and psoriasis.(45).

The other application is a genome-wide search for copy number variants (CNV) using a sample pooling approach. Zhang et al. (30) have identified a deletion comprising LCE3B and LCE3C, members of the late cornified envelope (LCE) gene cluster on 1q21. The absence of LCE3B and LCE3C (LCE3C_LCE3B-del) is significantly associated with risk of psoriasis in 2,831 samples from Spain, Netherlands, Italy and United States, and in a family-based study LCE3C-LCE3B-del is also strongly associated with psoriasis. (References) LCE expression can be induced in normal epidermis by skin barrier disruption and is strongly expressed in psoriatic lesions, suggesting that compromised skin barrier function has a role in psoriasis susceptibility. (Reference)

Gene expression

With many different technologies available for gene expression measurement (e.g. microarray, Real time PCR), the need to compare the results obtained from different platforms and technologies and thus the reliability and biological significance of those results becomes evident. Moreover, concerns regarding the reliability and consistency of the microarray technology from different suppliers, different test sites and when using

different methods for data processing and normalization have been raised. (Reference)

Microarray Technology

Multiple different microarray technologies can be used for studying either DNA or RNA with the purpose of identifying and explaining the role of genes involved in different processes. This powerful new technology is emerging, using hybridization to nucleotide arrays, the so-called (DNA) gene chips. (46-47) The technological intersection of biology and computers enables the reliable screening of a vast number of genes simultaneously and is amenable to automation. On a nylon membrane, quartz or glass surface, gene specific DNA molecules are printed on the chips as probes at regularly spaced and well defined locations called spots, or oligonucleotides can be synthesized in situ by a combination of photolithography and oligonucleotide chemistry. The hybridization signal is scanned with a fluorescent imager, which produces an image with red, green and yellow spots. (48) A green spot indicates that the corresponding gene was more highly expressed in the test sample than in the reference sample, while a red spot indicates the opposite. Some authors call the molecules on the chip as 'targets' and the molecules in the sample as 'probes'. This permits simultaneous monitoring of the expression of thousands of genes in a single step. Individual chips can be customized to include any chosen set of fully or partially characterized genomic or expressed sequences. Chips can monitor over 50000 unique sequences. (49) Modern High-Density Oligonucleotide Microarrays are characterized by their high number of spots or feature locations, concentrated on a small surface. Experimentally, DNA microarray is composed of five discrete steps: [1] fabrication of the DNA microarray, [2] preparation of the biologic sample, [3] hybridization of the labeled nucleic acid sample with the array, [4] signal detection and data visualization, and [5] data processing and analysis. (50)

Researchers have applied them to identify gene functions, to define genetic signatures of diseases, to understand genetic causes of diseases, and to characterize the effects of certain drugs on gene expression. (51) It provides the researcher with a new arsenal to analyze underlying pathomechanisms on a grand scale and also to review the rationale of therapeutic concepts. It is hoped that correlating gene expression data with other information, such as transcription factor binding site locations, (52) will give further insights into cellular pathways. DNA chips were originally developed for sequencing by hybridization (SBH), which has never been commercially successful on a large scale. A related application is the determination of SNPs, where a single base at a well-defined location differs across individuals. (53-54) For each SNP, the DNA chip contains four probes, enumerating all four possibilities at their center location. It is also possible to genotype human individuals with DNA chips. Different forms of a gene are called alleles; each individual has two alleles of most genes. The genotype is called homozygous if both alleles are identical, and heterozygous if they are different. DNA chips allow the determination of the genotype. (55)

a. The major applications of microarrays:

The major applications of microarrays fall into three groups: (56)

- 1. Gene expression profiling**—RNA extracted from a complex sample (such as body tissues or fluids or bacterial isolates) is applied to the microarray. The result reveals the level of expression of tens of thousands of genes, effectively all the genes in the genome, in that complex sample. This result is known as a gene expression "profile" or "signature."

2. **Genotyping**—Genomic DNA, extracted from an individual's blood or saliva, is amplified by the polymerase chain reaction and applied to the microarray. The genotype for hundreds or thousands of genetic markers across the genome can be determined in a single hybridisation. This approach has considerable potential in risk assessment, both in research and clinical practice.
3. **DNA sequencing**—DNA extracted from an individual's blood is amplified and applied to specific “re-sequencing” microarrays. Thousands of base pairs of DNA can be screened on a single microarray for mutations in specific genes whose normal sequence is already known. This greatly increases the scope for precise molecular diagnosis in single gene and genetically complex diseases.

b. Application of DNA microarrays in dermatology:

Gene expression profiling of normal skin is prerequisite to an understanding of gene expression data in inflammatory dermatoses. However, few studies of gene expression in normal human skin performed with DNA microarrays are available. On a DNA microarray containing about 4,400 genes, only 71 genes (1.6%) were variably expressed in normal human skin. (57) The genes coding for transport proteins, gene transcription factors, cell signaling proteins, and cell surface proteins belonged to this small group of genes that displayed substantial variability in their expression in normal human skin. This may help, however, in identifying those genes that are differentially expressed under pathologic conditions. Studying gene expression of normal human skin via the high-throughput approach of

DNA microarrays also allows the identification of new biomarkers or signature genes. (58) It is likely that some biomarker genes may be useful in molecular or immunohistochemical diagnostics or as molecular targets for drug discovery and therapeutic intervention. Recently, DNA microarrays that contain genes relevant to dermatology and dermatopathology are commercially available and marketed under the name DermArray (IntegriDerm, Birmingham, Ala). (47-59)

Quantitative real-time-PCR:

Quantitative real-time-PCR, though lacking the scale of microarrays, is a rapid, sensitive and less complex method for gene expression analysis and offers an alternative approach for parallel profiling of multiple targets as well as a time-saving means to validate microarray results. (60)

The TaqMan assay is based on real-time PCR using a fluorescent dye to monitor the amplification of target genes via the generation of a fluorescent signal in each round.

In addition, real-time PCR is widely considered the gold standard for gene expression measurement due to its high assay specificity, high detection sensitivity and wide linear dynamic range. In addition to the TaqMan assay, the SYBR Green PCR assay is another commonly used real-time PCR technique which is employed by half of all real-time PCR users. (61)

On the other hand, there are many techniques for measuring gene transcription focus on the quantitation of mRNA molecules, one of them is referred to reverse transcriptase polymerase chain reaction (RT-PCR). Most of these experimental techniques, however, focus on a single gene or a few genes at a time. In addition, northern blot analysis can be used to

determine how strongly a gene or splice variant is transcribed in a certain tissue or under specific conditions. The elevated expression of Psoriasis susceptibility related RNA Gene Induced by Stress (PRINS) in psoriatic uninvolved epidermis was further confirmed by real time PCR analysis performed on several independent samples. Real time reverse transcription-PCR analysis showed that PRINS was expressed higher in the uninvolved epidermis of psoriatic patients compared with both psoriatic lesional and healthy epidermis, suggesting a role for PRINS in psoriasis susceptibility. (62)

The pathomechanisms of psoriasis are complex and involve secretion of a variety of immunomodulatory chemokines. (63) In recent years, additional knowledge about the pathomechanisms involved in psoriasis came from studies on functional genomics, that is, RNA expression profiling. The transcriptome from skin biopsies was analyzed on microarrays containing more than 7,000 (50), 12,000, 12,000 oligonucleotide, or 63,000 oligonucleotide probe sets, or on cDNA arrays. (64,65,66) These studies consistently found differential expression of genes related to regeneration, hyperkeratosis, metabolic function, immune response, and inflammation in lesional psoriatic skin. In addition, the majority of induced genes in affected and unaffected psoriatic skin were involved with interferon mediation, immunity, cell adhesion, cytoskeleton restructuring, protein trafficking and degradation, RNA regulation and degradation, signaling transduction, apoptosis and atypical epidermal cellular proliferation and differentiation. The disturbances in the normal protein degradation equilibrium of skin were reflected by the significant increase in the gene expression of various protease inhibitors and proteinases, including the induced components of ATP/ubiquitin-dependent non-lysosomal proteolytic pathway that is involved with peptide processing and presentation to T

cells. (66) A range of signaling pathways was found to be modulated in psoriatic plaques. The microarray and biostatistical methods revealed, approximately, 10% of 179 differentially expressed genes were directly or indirectly related to the canonical Wnt/b-catenin or to the non-canonical Wnt/Ca2 pathway, indicating that Wnt pathways may be involved in the pathophysiology of psoriasis. The expression of Wnt5a was 4-fold higher in lesional skin. Other Wnt molecules were largely unchanged (Wnt4 and Wnt16), or tended to be expressed at lower levels (Wnt7b). These findings were confirmed by quantitative reverse transcription-PCR experiments and concluded that Wnt5a and other Wnt pathway genes are differentially expressed in psoriatic plaques. (67) Several genes that show increased expression in psoriatic plaques include the activator protein (AP)-1, AP-2, or Sp-1 promoter binding sequences in their promoter regions, for example, the hyperproliferation-associated keratins 16 (AP-1 and Sp-1) and 17 (AP-2 and Sp-1).

Among 177 differentially expressed genes identified as potential psoriatic markers (66), S100 calcium binding proteins showed the largest expression difference between involved and uninvolved skin in comparison to normal skin. Other transcripts up-regulated in both involved and uninvolved skin were transcobalamin I (vitamin B12 binding protein), CD47, IL8, ECGF1, SPRR2C and STAF50. As well as Affymetric arrays, 159 differentially expressed genes were identified as potential psoriatic markers. Zhau et al. (68) used a U95A microarray with which they generated a list of 1,338 genes that are potentially psoriasis related. About 60% of these encode newly discovered proteins and many of them possibly regulate the spatial organization of T cells and dendritic cells (DCs) to maintain T-cell activation within the involved and uninvolved psoriatic skin. In a study to determine the difference in gene

expression between psoriatic and normal skin, Kulski et al. (67) found that the number of significantly up-regulated genes were 102 in unaffected skin and 263 in affected psoriatic skin. Of the 263 up-regulated genes in psoriatic patients, 99 were up-regulated in both the affected and unaffected psoriatic skin and 164 were up-regulated in affected but not in unaffected psoriatic skin. The three genes up-regulated in unaffected but not in affected skin were degenerative spermatocyte homolog, lipid desaturase (DEG5), metallothionein IV (MT4) and perilipin (PLIN). The top seven upregulated genes based on their t-test ranking were ALOX12B, EIF5, CTSC, CDC42EP1, HDGF, MX1 and ITM2B in unaffected psoriatic skin and SYNCRIP, MYO5A, ALOX12B, UBE2L6, NAPA, TGM1 and SPRR1A in affected psoriatic skin.

The top 10 functional categories, based on 10 or more induced genes within a functional category, were genes coding for protein degradation (37 genes), IFN responses (23 genes), phosphatases and kinases (22 genes), binding proteins and transporters (18 genes), mitogen-activated responses (16 genes), epidermal differentiation (16 genes), RNA binding, regulation, and degradation (15 genes), cytoskeleton organization, myosin and actin-related protein 2/3 complex (13 genes), apoptosis (11 genes) and cell adhesion and interaction (10 genes). The protein degradation category contained four main subcategories of genes encoding proteinases (12 genes), proteasome components (10 genes), ubiquitination factors (8 genes) and proteinase inhibitors (7 genes). Other categories of interest include antioxidant/ antistress factors, heat responses/chaperones, signal transduction/ intracellular signaling and immune- and inflammatory- related factors. The functions for 4 genes were unknown. This study by Kulski et al. (67) also found that the number of significantly down-regulated genes

in psoriatic skin, while comparing these results to Affymetrix studies, it was noted that only 5 up-regulated genes (PSME2, FABP5, STAT1, TGM1 and IFI27) were reported to be common in all studies. Only 10 of the 51 up-regulated genes were found in Japanese psoriatic patients (JUNB, YWHAB, SEC61G, OAS1, CCL20, SEC61B, H2AFY, P4HB, RER1 and YWAQ). Moreover, the three up-regulated genes—YWHAB, YWHAG and YWHAQ have not been previously associated with psoriasis. The up-regulated genes reported by Bowcock et al. (66) and Oestreicher et al. (52) but not by Kulski et al. (67) include some previously well described psoriatic marker genes, such as S100A7, SKALP, CRAB2, KRT17, KRT18, DEFB2, SPRR2A and SPRRB1B. Furthermore, although Kulski et al. (67) and Oestreicher et al. (52) found that the SULT2B1 gene was significantly overexpressed in psoriatic lesions.

Further attention was turned toward immune signaling cascades, and 131 genes with differential expression were found. Involvement of LI-1H1 and IL-1HY1 (interleukine-1 family member5) in psoriasis was also confirmed with RT-PCR. Nineteen chemokines were determined to be differentially expressed, and 11 of these were described in relation to psoriasis for the first time. Zhou et al. proposed that expression of CCR7 leads to the entry of T cells into psoriasis lesion. (68) Chemokines and chemokine receptors of interest in the immunopathogenesis of psoriasis include TARC (CCL17), MIG (CXCL9), IP10 (CXCL10), MDC (CCL22), and RANTES (CCL5), as recently reviewed by Krueger et al. (69) Some other chemokines involved in the immunopathogenesis include CXCR2, CXCR3, CCR4, CCL27-CCR10, MIP3 (CCL20), MIP3(CCL19), and CCR6. In addition, nitric oxide is present, which may contribute to an angiogenic tissue reaction,

accompanied by many growth factors present at elevated levels within psoriatic plaques, including TGF-gama, IGF-1, keratinocyte growth factor (KGF), VEGF, nerve growth factor (NGF), amphiregulin, and IL-20. (69) Given the plethora of these cytokines, chemokines, and growth factors, it should not be surprising that the end result is a thick, erythematous scaly plaque in psoriasis. In general, activated CD4+ T cells are primarily located in the dermis and CD8+.

In conclusion, genotyping of single nucleotide polymorphisms, copy number variations and statistical tools have become extremely important to researchers for understanding the pathogenesis and molecular mechanism of psoriasis. Microarray analysis of psoriasis patients highlights the variability in gene expression occurring between individual patients, probably on the basis of their age, ethnicity, sex, genetics, skin types and environmental influences. The gene expression data and their analyses have suggested that psoriasis is a chronic interferon- and T-cell-mediated immune disease of the skin where the imbalance in epidermal cellular structure, growth and differentiation arises from the molecular antiviral stress signals initiating inappropriate immune responses.

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Legends:**Table.1 Candidate Loci in Psoriasis Identified by Genetic Linkage Studies**

Locus name	Chromosomal region	Associated gene	Source
PSORS1	6p21.3	HLA-C, HERV-K, HCG27, CDSN, PSORSIC3, POU5F1, TCF19, CCHCR1, LMP, SEEK1, SPR1	Saneczko et al.,15 Ishihara et al.,70 Trembath et al.13 Nair et. al., 29 Oka et al, 71 Veal et al.,72 Foerster et al.,73 Zhang et al.,75 Sagoo, et al.,76 Lee et al.,77
	6q	ND	Asumalahti et al.,78
	8q	ND	Trembath et al.,13
	10q	ND	Nair et al., 12
	14q	ND	Veal et al.,72 Bhalerao et al.,80
	15q	ND	Samuelsson et al., 81
	16q	ND	Nair et. Al., 79 Karason et al.,82
PSORS2	17q24-25	SLC9A3R1, NAT9	Helms et al.,26 Nair et al., 12 Samuelsson et al., 81 Tomfohrde et al.,24 Zhang et al.,30 Enlund et al.,83 Tiilikainen et al 84
	18P11	ND	Asumalahti et al.,78
	19P13	JunB	Lee et al.,77 Zenz et al.,85
	20P	ND	Trembath et al.,13 Nair et al.,79
			Matthews et

PSORS3	4q43	IRF-2	al.,86 Foerster et al.,74
PSORS4	1q21	S100, SPRR, PGLYRP3, PGLYRP4, IVL, PRR9, LCE.	Kainu et al.,27 Chen et al.,28 Zhang et al.,30 Bhalerao and Bowcock,80 Capon et al.,87
	2p	ND	Bhalerao and Bowcock,80 Veal et al., 72
	2q	ND	Trembath et al.,13
	3p	ND	Samuelsson et al.,81
PSORS5	3q	SLC12A8	Samuelsson et al.,81 Enlund et al.,83
	4q13	ND	Bhalerao and Bowcock,80 Samuelsson et al.,81
PSORS6	19p13-q13	ND	Veal et al.,72
PSORS7	1p34-p35	ND	Veal et al.,72
PSORS9	4q31	ND	Zhang et al.,30 Sagoo et al.,76

ND= not determined

Table.2 :Examples of some gene polymorphisms with psoriasis patients

Gene	Source
STAT4 (signal transducer and activator of transcription 4)	Zervou et al.,89
ZNF313/RNF114	Capon et al., 88
eNOS (endothelial nitric oxide synthase)	Senturk et al.,90
Retinoid X receptor	Vasku et al.,92
Antigen processing LMP; transport genes TAP	Kramer et al.,93
VDR (vitamin D receptor)	Dayango-Erden et al.,94
ACE (Angiotensin converting enzyme) gene	Veletza et al., 95 Weger et al.,96
MCP-1 (monocyte chemoc attractant protein-1)	Wang et al.,97
CTLA-4	Luszczek et al.,99
Leptin 1	Senturk et al.,91
Flaggrin gene	Chang et al.,100
VEGF gene	Wang et al 98., Lee et al.,77
VEGF receptor	Lee et al.,77
Pglyrp3 and Pglyrp4 (Peptidoglycan recognition proteins)	Sun et al.,101
POU5F1	Chang et al.,102
MTHFR C677T (methylenetetrahydrofolate reductase)	Bienertova-Vasku et al., 103
ApoE (Apolipoprotein E)	Campalani et al.,104
ADAM33 (A Disintegrin and Metalloproteinase 33), in CDKAL1(cycline-dependent kinase 1) PTPN22 (Lymphoid-specific protein tyrosine phosphatase, non-receptor type 22)	Li et al.,105
NAT2 (Ruacetyltransferase 2)	Kozhekbaeva et al.,106
NF-κB (Nuclear factor-kappa B)	Li, et al .,107
SUMO4 (Small ubiquitin-related modifier4)	Li, et al.,107

Table.3: List of cytokines involved in psoriasis pathogenesis with chromosomal location

Cytokines	Chromosomal region	References
IL-1 family	2q13	Nicklin et al.,108
IL-18	11q22.2-22.3	Sims 109
IL-2	4q26-28	Fletcher et al.,110
IL-4	5q23-31	Frazer, et al.,111 Keegan et al., 112
IL-6	7p21	Kishimoto 113 Le and Vileek 114 Szepietowski et al.,115
IL-11	19q13.3-3q13.4	Mc Kinley et al.,116
IL-7	8q12-q13	Sutherland et al.,117
IL-8	4q12-4q21	Lizasa and Matsushima 118
IL-10,IL19,IL-20, IL-24	1q31.3	Gallagher et al.,119 Fickenscher et al.,120
IL-12p40	5q31-q33	Sieburth et al., 121
IL-12p35	3q25.33-q26	Litjens et al.,122
IL-23p19	12q13.2	NCBI (142)
IL-15	4q31	Krause et al.,123
IL-17	2q31 6p12	Moseley et al.,124 Kolls and Linden 125
TNF FAMILY	6p21.3	Goetz et al.,126 Makhatadze 127
INF gama	12q24.1	Trent et al.,128 Bureau et al.,129