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Review Article

Genome and Epigenomic Study of Psoriasis

Zheng Zhang[1], Xuejun Zhang[1,2,3,*]

[1]Department of Dermatology, Huashan Hospital, Fudan University, Shanghai, China.
[2]Institute of Dermatology, Department of Dermatology, The First Affiliated Hospital, Anhui Medical University, Hefei, Anhui, China.
[3]Key lab of Dermatology, Ministry of Education, Anhui Medical University and State Key lab of Dermatology Incubation, Hefei, Anhui, China.

Corresponding author: Xuejun Zhang, 81 Meishan Road, Hefei 230032, Anhui, China; Tel: +86-551-62922370; Fax: +86-551-65138576; **E-mail:** ayzxj@vip.sina.com

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Abstract

Genome-wide association studies (GWAS) of psoriasis have identified 86 susceptibility loci. Most of these loci are located in non-coding regions, which makes it difficult for researchers to determine the functional effect of these risk-associated variants. One hypothesis is that these single nucleotide polymorphisms (SNPs) cause changes in gene expression levels rather than changes in protein function. In this review, we will focus on advances in psoriasis genomics and introduce epigenomic approaches that incorporate functional annotation of regulatory elements to prioritize the disease risk-associated SNPs which are located in non-coding regions of the genome.

Keywords: *GWAS, psoriasis, SNP, epigenomic, ATAC-seq*

Psoriasis (Ps) is a common inflammatory skin disorder caused by genetic and epigenetic factors with various environmental triggers in predisposed individuals.[1] The first study that sought to illuminate the genetic architecture of psoriasis is based on linkage analysis. Up to now, nine different regions have been identified (known as Psoriasis Susceptibility (PSORS)1-9).[2] The PSORS1 locus maps to the Major Histocompatibility Complex (MHC) on chromosome 6p21, has been robustly validated in all examined cohorts. [2] PSORS2 and PSORS 4 have been found to show weaker linkage signals, [3,4] while linkage to the remaining PSORS regions (PSORS-3, -5, -6, -7, -8, -9) could not be replicated in independent studies.[2]

In the early 2000s, researchers witnessed important advances in the effort to catalogue human genetic variation and in the development of high-throughput genotyping technology. In 2009, we reported the first large GWAS in a Chinese population, identified a new susceptibility locus within the LCE gene.[5] By now, the number of susceptibility loci had grown to 86. Meanwhile, samples sizes grew at a steady pace, with the latest published GWAS reporting the analysis of 19,000 cases and 280,000 controls.[6] The candidate genes identified so far tend to cluster around immune pathways. These include antigen presentation (*HLA-C* and *ERAP1*), innate antiviral signaling (*IFIH1*, *DDX58*, *TYK2*, *RNF114*) and most notably, the interleukin 23 (IL-23)/T-helper 17 (T_H17) pathway.[7]

Genetic studies of psoriasis have revealed robust and reproducible signals that implicate genes involved in core immunologic processes,[8] but only a small number of these genomic segments span a single gene, with the majority encompassing multiple transcripts and some mapping to gene deserts. What is the most relevant path for psoriasis genetics research going forward? Finding more genes through ever-larger case-control studies, with smaller and smaller detectable effects, remains a useful pursuit, however, it has been proven that in addition to genetic predisposition factors, epigenetic factors also play a role in the onset and progression of Ps. Additionally, most noncoding risk variants, including those that alter gene expression, affect non-canonical sequence determinants which are not well-explained. Thus, it is of key importance to use epigenomics engineering to understand the pathogenesis of Ps, armed with the genetic information we have.

In 2016, we first present epigenome-wide association analysis in large samples size in Chinese Han Ps patients, identified nine skin DNA methylation loci for psoriasis. We found that 11 of 93 SNP-CpG pairs, composed of 5 unique SNPs and 3 CpG sites, presented a methylation-mediated relationship between SNPs and psoriasis. Which supported the evidence that DNA methylation can be controlled by genetic factors.[9, 10]

According to data, above 90% of index SNPs in the GWAS catalog that have been associated with specific diseases or traits lie within non-coding regions. This holds true even when we employ fine mapping techniques to pinpoint the location of these risk-associated variants. Besides, as we attempt to sift through the long list of SNPs, we require some criteria for determining which SNPs are most deserving of follow-up analysis. One such criterion is to determine whether a given SNP falls within a functional region of the genome. Recently, a great progress in genome-wide epigenomic technique, make large-scale epigenetic biomarker annotation of diseases possible, these techniques including (i) Bisulfite sequencing to determine DNA methylation at base-pair resolution, (ii) Chip-Seq to identify protein binding sites on the genome, (iii) DNasel-Seq /ATAC-Seq to profile open chromatin and (iv) 4C-Seq and HiC-Seq to determine the spatial organization of chromosomes.[11]

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One kind of functional SNP are the SNPs located in regulatory regions of the genome (regulatory SNPs). Recently, ATAC-seq, a method that employs an engineered Tn5 transposase to measure chromatin accessibility, has been used to define genomic maps of open chromatin. The entire set of DHSs (DNase-hypersensitive) includes promoter regions, distal enhancer regions, and sites of binding of structural TFs. Chip-seq and antibodies specific to histone modifications can be used to further refine the set of distal DHSs to include only active enhancers. Several studies have shown that index and corrected SNPs are enriched in enhancers, and several of these index SNPs created or disrupted TF motifs in the identified enhancers. [12]

Another way to identify risk-associated SNPs is to focus on the subset that show allele-specific gene expression differences, based on expression quantitative trait loci (eQTL). Which are defined as genomic regions that harbor one or more nucleotide variants that correlate with differences in gene expression.[13] For eQTL analyses, SNPs are mapped using a genotyping array and mRNA abundance is measured by RNA-seq using hundreds of samples from cell lines or tissues. Statistical methods are then used to associate SNPs with transcripts to identify eQTLs.[14] Expression associated SNPs can be statistically significantly associated with genes that are located in a genomic region near to or far from the SNP in question, named cis- and trans- eQTL separately. Most studies focus on cis-eQTL because trans-eQTL require multiple testing to gain statistical power.[15] One compensatory technique of finding genes affected by a risk-associated effect far away is Circular chromosome confirmation capture (4C-seq) assay or Hi-C.

The combination of methods discussed above offer a general methodology for the investigation of risk-associated SNPs in non-coding regions of the genome. One article which demonstrates this approach is "genetic determinants of co-accessible chromatin regions in activated T cells across humans" published in Nature Genetics. To understand how variants in non-coding regions modulate gene regulation in health and disease, the authors carried out ATAC-seq, RNA-seq and Hi-C, in T helper cells with a large sample size. They showed that 15% percent of genetic variants located within ATAC-peaks affected the accessibility of the corresponding peak (local-ATAC-QTLs). Local-ATAC-QTLs have their largest effects on co-accessible peaks, are associated with gene expression, and are enriched for autoimmune disease variants. This research shed light on the epigenomic study of autoimmune diseases.

Finally, we must bear in mind the overall rationale for the use of GWAS experiments. This is to help us better understand the complete set of genes which contribute to the predisposition to, and pathogenesis of Ps. We must be cognizant of the fact that non-coding SNPs can affect the expression of downstream genes both directly and indirectly. For this reason, multi-layered experimental designs, which include identification of risk-associated loci, genomic manipulation, and subsequent gene expression analyses are of particular importance as we continue to search for novel diagnostic and therapeutic targets.

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