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Summary

Genome-wide association scans have delivered on their promise of revealing susceptibility polymorphisms underlying common diseases. This comprehensive psoriasis study reports confirmation of previously identified genes, *HLA-C*, *IL12B* and *IL23R*, identifies several novel psoriasis loci and is the first to report psoriatic arthritis association on a genome-wide scale. Along with other recent studies, this work gives further evidence that IL-23 mediated signaling is a key component of both psoriasis and psoriatic arthritis pathogenesis. Importantly, this study provides evidence of a single SNP, 35kb upstream of *HLA-C*, which is stronger than Cw*0602 – the variant traditionally attributed to the MHC-linked psoriasis-susceptibility effect. Within this region, they also discover an independent SNP with very strong predisposing effects. SNPs in the *COG6* region and the *USP8-TNFAIP8l3* region are among novel psoriasis associations reported. In addition, a region showing linkage on chromosome 1q demonstrated association in the epidermal differentiation complex. Four SNPs over a 439kb region on chromosome 4q27, where *KIAA1109*, *ADAD1*, and two cytokine-encoding genes (*IL2* and *IL21*) reside, exhibit intriguing correlation with psoriatic arthritis although the signal strength is moderate. These results, while still preliminary, may substantially expand our knowledge of psoriasis and psoriatic arthritis genetics – opening new avenues of chronic inflammatory disease research.

Introduction

The breakthroughs of using naturally occurring polymorphic markers to interrogate the genome in a hypothesis-independent fashion, theoretical developments of linkage analysis fundamentals, and later advances in genotyping technology gave rise to stunning successes in mapping relatively rare diseases, primarily through large-scale studies of linkage throughout the late 1980s and 1990s, and continuing today. While these less frequent phenotypes, very often with rare monogenetic etiologies, yielded to this type of scientific inquiry, common diseases such as psoriasis were much more reluctant to reveal their underlying genetics through linkage. Faced with this impediment, several researchers suggested a new path to uncover the relatively frequent variants underlying prevalent diseases. Arguing that the power of association-based designs to map common susceptibility alleles is high compared to linkage approaches, several researchers including Jorde, Risch and Merikangas, and Long, Grote and Langley helped motivate the recent wave of genome-wide disease association studies. While linkage-based studies rely on recombination events occurring in families, association-based approaches largely depend on historical recombination within populations. The result of this is that association studies enjoy substantial power to identify higher frequency polymorphisms of weaker effects, but require a high density of markers to interrogate the genome when compared to linkage studies. In addition, affected individuals are often easier to obtain under a case-control design when compared to pedigree-based experiments. Building on association mapping theory and propelled by technological developments in hybridization arrays, high-throughput PCR-based genotyping and sequencing, genome-wide genetic architecture studies and analysis advances in multiple testing, population stratification and linkage disequilibrium, genome-wide association studies have become a reality over the past four years. These studies have recently transformed common, complex disease mapping resulting in a large number of convincing susceptibility polymorphisms across a wide spectrum of common diseases, including psoriasis.

Worldwide, psoriasis is the most common systemic autoinflammatory disorder affecting 0.5-3% of the general population. The disease is typified by overproliferation of keratinocytes and recruitment of immunocytes, including CD4+ T lymphocytes, to the dermal tissues generating chronic inflammation. Affecting joints and surrounding tissues in ~25% of psoriatic patients, inflammatory arthritis markedly impacts mobility and can cause irreversible joint destruction. Interestingly, several genetic and epidemiological studies have demonstrated that Crohn's disease, cardiovascular disease and metabolic syndrome are co-morbid with psoriasis, particularly with more severe, earlier onset psoriasis. The recent genetic association findings

have strengthened the case that psoriasis and Crohn's disease have overlapping etiologies; and suggest some underlying correlation between psoriasis and other autoinflammatory diseases such as Graves' disease and ankylosing spondylitis. The apparent cardiovascular disease and metabolic syndrome associations with psoriasis remain an enigma but given the extensive genome scan work for these indications, perhaps light will be shed on these comorbidities in the near future.

The application of the SNP-based, genome-wide association approach to psoriasis has bore much fruit and a recent study by Liu and colleagues is no exception. Testing over 300k SNPs across the genome, Liu and colleagues [1] have conducted a dense, large-scale screen using multiple sample sets to discover regions associated with psoriasis and psoriatic arthritis. Although the study conducted by Liu and colleagues follows two recent psoriasis genome-wide association scans [2,3], there are many unique aspects to this study and several novel results: The focus on both psoriasis and psoriatic arthritis and the reporting of significant markers across the genome are major scientific contributions of the Liu *et al* study. Not only does this study report confirmation of previously reported psoriasis-susceptibility SNPs residing in genes involved in the IL-23 signaling pathway, *IL12B* and *IL23R*, but the investigators present new association signals in the major histocompatibility complex (MHC), novel findings of *IL12B* and *IL23R* associations with psoriatic arthritis, two chromosome 13q13-linked SNPs within (intron 1) and 24kb downstream of *COG6* (part of the oligomeric golgi complex), two 15q21-linked SNPs in a region carrying *TNFAIP8L3*, and an interesting psoriatic arthritis association on chromosome 4q27 which carries the type I cytokine-encoding genes *IL2* and *IL21*.

Keywords

Psoriasis, Psoriatic Arthritis, SNP, genetic mapping, genome-wide association

Methods & results

Liu and colleagues chose a multi-stage, case/control experimental design with individuals from the USA and the UK of European descent, supplemented by a single family based sample set to perform transmission tests (see Figure 1). Initially, 311k SNPs were screened in a small to moderate sized sample set and this was pared down to 306k following thorough quality control procedures. The study was designed to interrogate psoriatic individuals both with and without psoriatic arthritis. Three additional, independent sample sets (two case/control sets and one family-based set) were used to screen 120 regions of interest obtained from the initial scan. This reduction in the number of markers evaluated, provided by the staged design, aids in reducing the

multiple testing burden of the study. To investigate the potential confounding effects of population stratification, the researchers performed two commonly-used methods. In sum, they find little evidence for population stratification in their samples and adjust for diffuse effects of population stratification using a genomic control approach. While there are now techniques which are considered preferable to this approach [*e.g.* 4], I would judge the impact of errors made by using these genomic control-adjusted results to be minimal. The use of multiple stages also decreases the likelihood of false positives resulting from population stratification, and the confirmation of well-established markers as positive controls lends further credibility to their design and results. The statistical methods used to test for psoriasis association are standard and appropriate.

This study has both confirmed previous findings as well as generated several novel association results for both psoriasis and psoriatic arthritis. The broad association signal across the MHC region verifies numerous previous linkage and association findings. Further dissecting these results, the authors show several important features of the association peak. Through their experiments, Liu and colleagues demonstrate that a single SNP, rs10484554, located 34.7kb upstream of *HLA-C*, exhibits a stronger psoriasis-predisposing result ($P_{comb} = 1.8x10^{-39}$) when compared to the classic HLA-Cw*0602 allele. The T allele of this SNP marks haplotypes carrying the Cw*0602 and Cw*1203 variants. Not only does this finding likely simplify future genotyping efforts, but it also adds to the mounting evidence that *HLA-C* and not other 6p-linked genes such as *CDSN* and *HCR* – albeit excellent candidate genes – is primarily responsible for the MHC-linked (PSORS1) effect [5]. Moreover, there appears to be an additional polymorphism, rs2395029, within the *MICA-MICB* region in an immune-related gene *HCP5*, which exhibits a strong susceptibility effect, independent of rs10484554. Both of these MHC SNPs are also significantly associated with psoriatic arthritis, although not as strongly as psoriasis. Only population-based, linkage disequilibrium studies enable this type of resolution. Although not performed in this study, it would be extremely interesting and potentially very useful to explore the combined effect of these two MHC SNPs. The authors also confirm previously-described *IL12B* and *IL23R* SNPs as being associated with psoriasis; and their sample collection and design allowed them to extend past studies and provide the first report of these important SNPs being involved in psoriatic arthritis susceptibility. The work also purports a novel SNP association 4kb upstream from *IL12RB2*, a gene neighboring *IL23R* and an excellent psoriasis candidate gene, independent of previously reported SNPs in *IL23R*. However, the analysis of this SNP conditioned on rs11209026 (a strongly associated, replicated *IL23R* SNP for psoriasis and

pleiotropic for other autoimmune diseases), is not entirely convincing. Further, this 4kb upstream-*IL12RB2* SNP does not show significant association with psoriatic arthritis.

Although replication studies are needed, the novel regions arising from this study are intriguing. Notably, the authors describe new psoriasis findings for SNPs flanking the *COG6* gene (combined P-values of $1x10^{-5}$ and $2x10^{-6}$; OR ~ 1.4), the *USP8-TNFAIP8L3* region on chromosome 15q21 (combined P-values of $5.6x10^{-5}$ and $2.9x10^{-5}$; OR ~ 1.4), and within the 1q21 *LCE* gene cluster on the rapidly evolving [6] Epidermal Differentiation Complex which sits under a putative linkage peak (combined P-value of $5x10^{-4}$; OR ~1.5). The *COG6* results are interesting as the COG complex may perform a role in glycosylation of ADAM proteases and *ADAM33* is a recently replicated psoriasis [7, 8] and asthma [9] susceptibility gene. The 15q21 region arouses similar interest. The authors note the work by Friedmann and colleagues [10] as lending considerable weight towards a gene within this region, *SPPL2A*, which encodes a protease that mediates the intramembrane cleavage of TNFα, triggering IL-12 expression in dendritic cells. While this is an excellent candidate, the genetic evidence presented appears to more strongly favor another gene, *TNFAIP8L3*. Even though the function is not known, *TNFAIP8L3* contains a highly-conserved DUF758 domain found to be induced by TNFα in other proteins. For both the *COG6* and 15q21 regions, it is comforting to see more than one strongly-associated SNP. Lastly, the signal on 1q21 suggests a precursor of the cornified envelope of the stratum corneum, *LCE1C*, or perhaps the neighboring and related gene, *LCE3A*. Along with replication studies, follow-up studies using fine mapping techniques are necessary to verify and hone these new results. In addition, gene-specific re-sequencing efforts in cases may shed light on low frequency genetic alterations that may contribute to disease susceptibility. If the underlying linkage disequilibrium structure dictates, refinement of each of these association signals to a single gene or functional motif is needed so that keenly focused functional studies can provide a mechanistic understanding of their potential role in psoriasis.

Although not overwhelmingly strong, the most compelling non-MHC region found for psoriatic arthritis was 4q27. Although other psoriasis studies have found linkage on the long arm of chromosome 4, these linkage peaks do not overlap with this region on 4q27. Two cytokine-encoding genes lie within this region: *IL2* and *IL21*. The most significant SNP in this region, rs6840978, is upstream of the mRNA start site for *IL21*; however, there are additional significant SNPs that extend to the neighboring genes *KIAA1109* and *ADAD1*. As the authors point out, there is recent evidence that this region is involved in other autoimmune diseases: Type 1 diabetes, Graves' disease, Crohn's disease, Celiac disease and rheumatoid arthritis [11-14]. Also, IL-21 plays an important role in inducing upregulation of IL-23R on T cells, contributing to an

IL-23 response [15]. This finding follows a report of another type I cytokine, IL15, which appears to carry variants with psoriasis-predisposing effects [16]. However, two methodological issues arise for the 4q27 finding: 1) The authors appear to use the UK sample set as the discovery set for this finding, where in other parts of the manuscript these samples were used to replicate findings; and 2) The authors appear to attempt to replicate this finding with a comparison between psoriasis and controls, rather than psoriatic arthritis. That said, the authors do construct haplotypes and perform a multipoint transmission-based test using their psoriasis nuclear family sample set, yielding significant results (see Figure 1). Clearly, replication in independent psoriatic arthritis studies and psoriasis studies is necessary.

Discussion & significance

The results generated from Liu and colleagues as well as other genome-wide association scans hold promise in three exciting areas: 1) Understanding the degree of shared etiology across related disease phenotypes, 2) The use of replicated, associated markers in generating clinically relevant prognostics and 3) Providing insights into molecular pathobiology which may directly lead to remarkable progress in pharmacogenetics and therapeutic development.

For three decades, it has been well-understood that variants at the MHC are both linked and associated with autoimmunity, numerous inflammatory traits and infectious diseases. In a few sagacious meta-analyses, several groups of investigators suggested that non-MHC genetic factors clustered among T-cell mediated inflammatory diseases. Among the most comprehensive of these was a report by Becker and colleagues using data from genome-wide linkage studies [17]. Now with several genome-wide association scans having been performed on large sample sets, we now have detailed information on non-MHC susceptibility polymorphisms shared by autoimmune and autoinflammatory conditions. Liu and colleagues have furthered our understanding in this area by confirming psoriasis-associated SNPs in *IL12B* and *IL23R*, shown psoriatic arthritis-specific association to markers in these two genes, and have produced a novel psoriasis and psoriatic arthritis association on 4q27. The degree of pleiotropy corresponding to these three regions is nothing short of remarkable. A 3'UTR *IL12B* SNP was found to be associated with atopic dermatitis and psoriasis susceptibility [18], a functional promoter variant in *IL12B* is overtransmitted to children with cerebral malaria [19], numerous reports of *IL12B* 3'UTR variants being associated with mycobacterial infection [e.g. 20], *IL12B* haplotypes are associated with asthma susceptibility and severity [e.g. 21], *IL12B* polymorphisms associated with ulcerative colitis [22], and a *IL12B* 3' UTR SNP is possibly associated with subacute sclerosing panencephalitis patients resulting from measles infection [23]. Both *IL12B* and *IL23R*

polymorphisms are associated with adult-onset Crohn's disease [e.g. 24, 25], and *IL23R* SNPs have been shown to underlie pediatric Crohn's disease [e.g. 26], ankylosing spondylitis [e.g. 27] and Graves' disease with ophthalmopathy [28]. Clearly, delineating the degree of overlap for genetic susceptibility factors across diseases will inform the possibility of cross-utilization of existing therapeutics, the development of new, highly-targeted therapeutics and shed light on autoimmune etiology.

The most celebrated goal of the genomics revolution is the use of individual DNA variability to inform patient-specific medical decisions, or personalized medicine. One way to realize this central focus of medical research is through the calculation of an individual's disease risk given the patient's clinical information, levels of any relevant serum analytes and predictive genetic markers. For highly penetrant, monogenic diseases such as hereditary nonpolyposis colorectal cancer [29], familial breast and ovarian cancers [30], and familial hypercholesterolemia [31], genetic testing and subsequent treatment modification and/or intervention are currently performed. The status quo for common diseases such as psoriasis, however, substantially trails these Mendelian phenotypes. As with the advent of linkage mapping and genome-wide association scans, it is through an interplay of theory and experiment that this will be accomplished. Initial attempts at individualized prognostics have now begun. Citing a recent paper by Chang et al where polymorphisms at *HLA-C*, *IL12B*, *IL23R* and *IL13* were combined to generate an 11-fold range of psoriasis risk profiles [32], Liu and co-authors suggest that the addition of *COG6* and 15q21 variants could play a role in further modifying an individual's risk of psoriasis. In addition, as more genetic markers and other predictive factors become available, it may be possible to develop a diagnostic for psoriatic arthritis using *MHC*, *IL23R*, *IL12B*, and perhaps 4q27 alleles (if replicated) alongside arthrocentesis, sedimentation rates and other standard clinical tests.

Pharmacogenetics and therapeutic targets are central derivatives of genetic studies. Importantly, the genetic findings of this and other large-scale psoriasis mapping studies, particularly those of *IL12B* and *IL23R*, coupled with results from multiple areas of research ranging from molecular immunology to clinical biology have recently implicated the IL-23/T_H-17 pathway as being central to chronic inflammatory conditions such as psoriasis and inflammatory bowel disease (see Figure 2); the perturbation of which may disrupt the communication between the innate and adaptive immune responses. In sum, these studies demonstrate several key aspects of IL-23/T_H-17 pathobiology related to psoriasis: 1) Both IL12p40 and IL-23p19 mRNA expression levels are significantly elevated in both non-lesional psoriatic skin versus normal skin as well as lesional psoriatic skin versus non-lesional psoriatic skin [33, 34]. 2) IL-12 and IL-23

knockouts and IL23-deficient animal model experiments indicate that the systemic inflammatory effects, dermal inflammation and epidermal hyperplasia are often mediated through the IL-23/T_H-17 pathway [33, 35], 3) T_H17 survival and expansion, key characteristics of epithelial inflammation and epidermal hyperplasia, occurs in response to IL-23 [36-38], 4) IL-23p19 antibodies inhibit proinflammatory cytokines in a mouse model of inflammatory bowel disease [39], and 5) clinical studies have shown dramatic efficacy of IL-12p40 antibodies in reducing psoriasis symptoms in a high percentage of subjects [40, 41] and those with active Crohn's disease [42]. These diverse studies have conspired to highlight the central function of the IL-23/T_H-17 axis in mediating chronic inflammatory disease pathogenesis, downplaying the role of IL-12. These insights from genetics and functional biology will undoubtedly drive further targeted therapeutic development and corresponding dose/response prediction based on psoriasis susceptibility genotypes as well as pathway-specific genotypes. As a result, the safety and efficacy of pharmaceuticals treating chronic inflammation is likely to improve.

Five-year view

In terms of psoriasis genetics, and more broadly chronic inflammatory disease genetics, there is much work that lies ahead. The current large-scale SNP association scans represent the second generation of genome-wide genetic studies, with family-based linkage studies being the first. Studies of disease heritability strongly suggest a substantial genetic component of these psoriasis and psoriatic arthritis that has yet to be identified. Genome-wide screens of SNPs will provide insight into the genetic susceptibility component derived from common alleles having moderate effects. However, there is much more genetic variation in the human genome to investigate. The recent work discovering and unraveling the rich structural variation/rearrangements in the human genome may form the basis of the next wave of genome-wide studies. In fact, earlier this year investigators at the University of Leicester reported the first case-control genomic copy number at beta-defensin genes, demonstrating susceptibility to psoriasis [43]. And with the immense academic and commercial interest in low-cost, high-throughput whole-genome sequencing, it is not inconceivable that disease association studies using full genetic information might become a reality by 2013 or shortly thereafter. Finally, with the expectation that these common complex diseases could represent a heterogeneous mix of phenotypes with different, but overlapping underlying etiologies, analyses based on genetic background, in the presence of additional susceptibility variants, or dynamic biomarkers may result in more accurate disease risk predictions. A paradigm case for such a scenario is the association of the R620W polymorphism in *PTPN22* being restricted to affected individuals with RF-positive rheumatoid arthritis [44]. A

recent paper [45] highlighted the marked increases in risk possible with the identification of disease subsets.

A possible but generally underappreciated result of genetic studies of disease susceptibility is the potential for the very same SNPs to serve as pharmacogenetic response markers to discern patient groups who will differentially respond to specific therapeutic interventions. Examples of this include TCF7L2 [46] and KIF6 [47-49] for sulfonylureas in diabetes and statins for coronary heart disease, respectively.

The successes of population-based, genome-wide approaches such as that used by Liu and colleagues will undoubtedly spur on additional large-scale genetic studies in the immediate future. As with the Liu *et al*. study, new genome-wide psoriasis and psoriatic arthritis scans will play an important role in both confirming existing and generating novel associations. Meta-analyses across the three existing genome scans would also greatly enhance the signal strength from *bona fide* psoriasis loci. Theoretical results demonstrating the effectiveness of imputation schemes will enable useful cross-platform comparisons [50]. Expansion of functional biology efforts will undoubtedly stem from the results of these genome-wide scans. It is interesting to note that in the past when throughput for genetic studies was much more limited, functional studies were a large source of candidate genes to study through genetics. The situation is now reversed. As genome-wide scan results become available, those loci exhibiting high levels of statistical significance and replicating across well-powered studies will provide expansive fodder for those conducting molecular biology, cellular biology, immunology, pharmacology, systems biology and clinical research.

While these initial genome-wide scans cover a substantial fraction of the existing common SNP variation in the genome, much work will be required to obtain causative polymorphisms which may be in moderate to high linkage disequilibrium with initial association signals. It is not unusual for association peaks to cover regions beyond several hundred kb, involving numerous genes and other functional elements. Even though the current genome-wide scan panels are dense, they do not yet have sufficient SNP density (with many SNPs in moderate to high linkage disequilibrium) required to fully interrogate regions of interest. To dissect these complex patterns of linkage disequilibrium coupled with often-labyrinthine association signals, well-designed fine mapping and sequencing efforts are clearly needed. Additionally, as the majority of genome-wide studies thus far have principally concentrated on individuals of European descent, subsequent disease genetics work will need to expand to other ethnic groups. Not only will this provide broader application of results, but will aid further refinement of association signals. Finally, as genetic information is important but not completely conclusive,

subsequent functional experiments will typically be necessary to fully elucidate the molecular basis of disease pathogenesis.

Key issues

- Genome-wide association scans offer a new and successful approach to disease gene mapping.
- The use of high density SNP scans, coupled with a multi-staged approach using several, appropriately powered sample sets is a useful approach to identify common polymorphisms having moderate effect sizes.
- Novel psoriasis-association patterns were found in the MHC region. One SNP, rs10484554, is likely more highly associated than Cw*0602. Another SNP, rs2395029, might carry predisposing effects independent of rs10484554 and is located in *HCP5*.
- These MHC association signals further reduce the likelihood that nearby psoriasis candidate genes such as *CDSN* and *HCR*, play a role in disease pathogenesis.
- Confirmation of non-MHC psoriasis-susceptibility genes, *IL12B* and *IL23R*, providing additional evidence of IL-23 response playing a key role in chronic inflammatory disease.
- First finding of *IL12B* and *IL23R* SNPs being associated with psoriatic arthritis.
- Seven statistically compelling, novel psoriasis-predisposing regions identified including *COG6* and *TNFAIP8L3*. These regions await replication in independent studies.
- A novel psoriatic arthritis locus is reported on chromosome 4q27, with the most highly significant marker located in an intergenic region 5' of *IL21*. Although the statistical evidence is not conclusive, this is an important region that begs for additional independent studies testing psoriatic arthritis susceptibility.
- The study highlights some of genetic differences between psoriasis and psoriatic arthritis.
- Both further replication studies and fine mapping efforts are required to verify and refine these psoriasis and psoriatic arthritis association signals.
- These and other large-scale association findings may directly aid clinical practice through more effective prognostics, development of highly-targeted therapeutics, pathway-specific pharmacogenetic effects on dosage, safety and response, and an increased understanding of the shared etiology across autoinflammatory traits.

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Figure 1: Study Design.

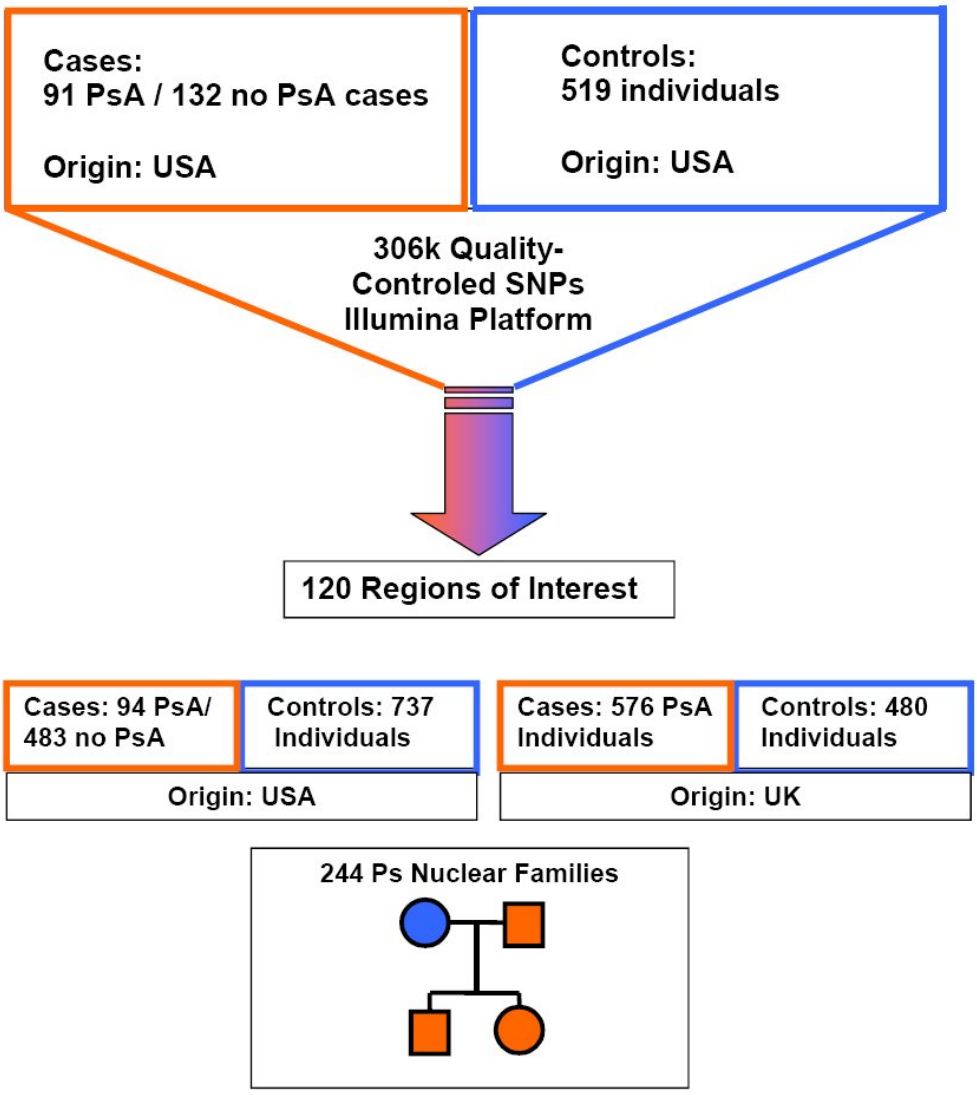

Figure 2: Psoriasis Genetics and IL-23 and IL-12 Signaling.