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Dissecting SLE Heterogeneity with Sub Phenotype Mapping

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Description

Systemic lupus erythematosus (SLE) is a complex, multifactorial autoimmune disorder in which environmental factors cooperate with multiple genetic variants in disease pathogenesis. It is a highly heterogeneous condition, characterized by differences in autoantibody profile, serum cytokines, and diverse clinical manifestations, making it difficult to predict the spectrum of organ-system involvement and long-term outcomes in an individual patient. It is evident from familial aggregation and monozygotic twin studies that SLE has a strong genetic component [1]. Recent advances in human genetic studies have advanced our knowledge of the immunopathogenesis and have explained some of the genetic basis of SLE [1,2]. Various candidate gene studies, genome wide association studies (GWAS) and large scale replication studies of SLE in different ancestral backgrounds have been successful in identifying more than 60 genetic risk factors and emphasizing their important role in SLE susceptibility [3]. However, they were able to explain relatively little of the heritability of this complex trait, accounting for far less than half of the heritability of SLE [2,4-7], and most of the variants identified through these studies have modest overall effect sizes (odds ratio (OR) ~1.2 to 1.5) [2,3].

There is a large degree of phenotypic and genetic heterogeneity in SLE makes it challenging to define the heritability of this disease. Different genetic variations and molecular pathways might have varying consequences in different patients. It is possible that some genetic associations are unique to a particular group of SLE patients based on the fact that certain genetic factors will be linked to specific disease phenotypes and pathogenic pathways [8-10]. We suspect this between-patient heterogeneity in the molecular pathogenesis of SLE is a key factor in the unexplained heritability of the disease to date. This heterogeneity among patients greatly reduces the power of overall case-control studies in SLE, and is a probable explanation for much of the "missing heritability" in this disease [11]. We suggest that it is feasible to directly study the genetic heterogeneity in SLE by designing studies focusing on pathogenic molecular subphenotypes. If these phenotypes truly represent differences in the root causes of the disease, then this method would greatly increase our power to detect novel pathogenic loci. Our recent SLE case-case GWAS study using the pathogenic molecular sub-phenotype interferon-alpha (IFN-α) is a good example of utilizing the sub-phenotype mapping strategy to identify additional important pathogenic SLE-associated genes which otherwise may be missed with standard case-control analyses [11].

IFN-α is a type I interferon with the potential to break self-tolerance by activating antigen-presenting cells [12], and is central to the pathogenesis of SLE. Circulating serum IFN-α levels are higher in SLE patients [13] and this IFN pathway activation is heritable within SLE families [14]. Case-control genetic studies in SLE have demonstrated remarkable overrepresentation of a number of genes involved in type I IFN signalling, production and response [2]. We have subsequently demonstrated that many SLE risk genetic polymorphisms contribute to high IFN levels in SLE patients [15,16] supporting the idea that gain-of-function polymorphisms in the IFN pathway are a common pathogenic mechanism in SLE. Previous work from our group has also shown that some of the established SLE-risk loci are characterized by strong subphenotype effects, which are much greater than the overall case-control effect size [2,17]. For example, >70% of the risk of SLE related to the IRF5 gene is found in a specific subset of patients defined by an autoantibody profile [17]. IRF5 is one of the strongest overall risk factors for SLE, suggesting that heterogeneity in genetic association may be a common phenomenon. To address heterogeneity directly and identify additional novel genetic factors associated with IFN pathway dysregulation in SLE, we performed a GWAS comparing high IFN SLE patients to low IFN SLE patients. This case-case subphenotype mapping strategy allowed us to detect genetic influences on serum IFN-α in SLE, thus identifying novel pathogenic SLE-associated genes which may not be detectable

with standard case-control studies. We studied over 1800 SLE cases from different ancestry using this approach and were able to identify a novel association between several new loci with high serum IFN (PMeta-analysis <x10-8) [1]. The top loci in our study have not been previously reported in other case-control studies of SLE, and were not top loci in the initial case-control analysis of the GWAS dataset we used in this study, supporting the potential of this approach to define new genes linked to SLE pathogenesis.

In an additional study, a similar case-case sub phenotype mapping approach was used to detect genetic factors associated with autoantibody profiles and serum IFN-α in moderate-sized well-characterized SLE cohort [18]. SLE-associated autoantibodies (anti-RBP and anti dsDNA) are another important heritable sub-phenotype in SLE that plays a pathogenic role in disease initiation [14,19]. In this study, a case-case GWAS was performed by stratifying patients with extremes of high vs. low interferon and presence vs. absence of autoantibodies, and this study design identified a number of novel genetic regions that are associated with high IFN-α and particular autoantibodies in SLE patients [18]. These genetic associations were very strong and specific to the particular patient groups and were not as strong in the overall cohort, again suggesting that this trait stratified approach was essential to discover these genes. These studies support the idea that distinct genetic associations underlie the heterogeneity of molecular pathogenesis in SLE. Apart from GWAS studies, sub phenotype mapping strategy has also been employed to compare peripheral blood gene expression between AA (African American) and EA (European American) SLE patients stratified by the presence or absence of anti-RBP antibodies [20]. In this study, the sub phenotyping approach helped to discover heterogeneity in the activation of molecular pathways between ancestral groups based on the presence of particular autoantibodies.

More recently the concept of subphenotyping has been applied to study SLE-associated renal disease, known as lupus nephritis (LN). LN is a common and severe complication of SLE that can advance to end-stage renal disease (ESRD), leading to an increased burden of morbidity and mortality [21]. Despite the discovery of numerous overall SLE susceptibility genes, only a small subset of these genes is associated with susceptibility to LN [22]. Additionally, the magnitude of the effect size (OR) for overall SLE susceptibility genes as risk factors for LN is much lower than their impact upon SLE in general indicating their broad impact more on SLE than their impact upon LN alone. To address this question, studies have examined the LN phenotype directly by comparing SLE patients that have LN to those without LN. This disease sub phenotyping strategy aided in discovering new genes with renal functions that specifically linked to LN but has not been discovered in overall case-control studies of SLE [23-25].

The above studies all support the idea that the sub phenotype mapping strategy can be an efficient method to identify novel genetic variants associated with SLE that are not readily apparent in case-control designs. In fact, these studies suggest that SLE is characterized by a complexity in genetic architecture that will require molecular sub phenotyping to fully delineate. Secondly, this approach can help to characterize the molecular heterogeneity in SLE immune pathway activation that may be clinically important, such as IFN-pathway activation. This pathway is currently being targeted therapeutically, and heterogeneity in patient response may be tied at least in part to genetic heterogeneity in type I IFN pathway. The next major frontier is in understanding the molecular and immunologic significance of the genetic variations that are associated with SLE, as this type of knowledge will allow us to personalize treatment.

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