Journal of Autoimmunity xxx (2015) 1–11

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Review article

Immunogenetics of juvenile idiopathic arthritis: A comprehensive review

Aimee O. Hersh [a], Sampath Prahalad [b, c, *]

[a] University of Utah School of Medicine, Salt Lake City, UT, USA
[b] Departments of Pediatrics and Human Genetics, Emory University School of Medicine, Atlanta, GA, USA
[c] Children's Healthcare of Atlanta, Atlanta, GA, USA

ARTICLE INFO

Article history:
Received 4 August 2015
Accepted 5 August 2015
Available online xxx

Keywords:
Juvenile idiopathic arthritis
Genetics
Association
Immunochip
Candidate gene
Genome-wide association studies

ABSTRACT

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory arthropathy of childhood. Juvenile idiopathic arthritis is believed to be a complex genetic trait influenced by both genetic and environmental factors. Twin and family studies suggest a substantial role for genetic factors in the predisposition to JIA. Describing the genetics is complicated by the heterogeneity of JIA; the International League of Associations for Rheumatology (ILAR) has defined seven categories of JIA based on distinct clinical and laboratory features. Utilizing a variety of techniques including candidate gene studies, the use of genotyping arrays such as Immunochip, and genome wide association studies (GWAS), both human leukocyte antigen (HLA) and non-HLA susceptibility loci associated with JIA have been described. Several of these polymorphisms (e.g. *HLA class II*, *PTPN22, STAT4*) are shared with other common autoimmune conditions; other novel polymorphisms that have been identified may be unique to JIA.

Associations with oligoarticular and RF-negative polyarticular JIA are the best characterized. A strong association between *HLA DRB1:11:03/04* and *DRB1:08:01*, and a protective effect of *DRB1:15:01* have been described. *HLA DPB1:02:01* has also been associated with oligoarticular and RF-negative polyarticular JIA. Besides *PTPN22*, *STAT4* and *PTPN2* variants, *IL2, IL2RA, IL2RB*, as well as *IL6* and *IL6R* loci also harbor variants associated with oligoarticular and RF-negative polyarticular JIA. RF-positive polyarticular JIA is associated with many of the shared epitope encoding *HLA DRB1* alleles, as well as *PTPN22, STAT4* and *TNFAIP3* variants. ERA is associated with HLA B27. Most other associations between JIA categories and HLA or non-HLA variants need confirmation. The formation of International Consortia to ascertain and analyze large cohorts of JIA categories, validation of reported findings in independent cohorts, and functional studies will enhance our understanding of the genetic underpinnings of JIA.

1. Introduction

Juvenile Idiopathic Arthritis (JIA), also previously termed Juvenile Rheumatoid Arthritis (JRA) or Juvenile Chronic Arthritis (JCA), is the most common chronic arthropathy of childhood and affects hundreds of thousands of children in the United States and around the world [1]. It is a serious disorder of childhood with potentially devastating consequences for the individual and society. JIA has the potential to disrupt growth, and adversely affect the joints resulting in permanent joint damage and long-term functional limitation and disability. Most children with JIA continue to have active disease years after onset, and in the majority of cases, the disease persists into adulthood, dispelling the notion that children can "outgrow" JIA [2,3]. Furthermore, JIA is associated with a substantial economic burden [4].

2. Overview of JIA genetics

JIA is believed to be a complex genetic trait influenced by both genetic and environmental factors [5]. There is substantial evidence for genetic contribution to JIA. Twin and affected sibling pair studies have supported a role for genetic susceptibility to JIA. Twin studies have shown that the monozygotic twin concordance rates for JIA range between 25 and 40%, a risk that is substantially greater

* Corresponding author. Emory University School of Medicine, 1760 Haygood Dr. NE, Atlanta, GA 30322, USA.
E-mail address: sprahal@emory.edu (S. Prahalad).

http://dx.doi.org/10.1016/j.jaut.2015.08.002
0896-8411/

than the population prevalence of 1 in 1000 [6–8]. In the largest twin study from the JIA affected sibling pair registry, 14 pairs of twins concordant for JIA were analyzed [9]. Of the 14 pairs of twins, one was discordant for gender and the rest were same-sex twins. All 13 pairs were concordant for onset and course. Twelve were concordant for presence/absence of anti-nuclear antibodies. The first twins to develop JIA did so a mean of 5.5 months before the second twins. In contrast, among the 104 non-twin affected sibling pairs in the registry, the difference in age at onset between the first and second sibling was 37 months, which was statistically different compared to twins. DNA was available on 11 twin pairs and all 11 were found to be monozygotic, in contrast to one third that were expected to be monozygotic based on the occurrence of twinning in the USA. Together, these twin studies provide strong evidence for genetic factors contributing to the susceptibility to JIA.

Affected sibling pair studies have also been carried out in JIA. Examination of the phenotypes of siblings affected with JIA has shown that sibling pairs were significantly concordant for sex, onset type and course type of JIA [10]. This was confirmed in a larger analysis of 164 sibling pairs [11]. Siblings were more likely to develop disease at the onset age, rather than calendar year. With the exception of number of joints at onset among children with polyarticular JIA, other clinical features did not differ between sporadic and multiple JIA cases.

Family studies can also provide evidence for genetic contribution to JIA. Although traditional multiplex families with numerous affected cases of JIA have been only rarely described, innovative approaches using a probabilistic record-linking of records in a JIA registry to the Utah Population Database have resulted in the identification of extended multiplex pedigrees with multiple affected individuals with JIA [12,13]. This approach identified 22 founders who had a significantly increased number of descendants with JIA (5–13 descendants) compared to what would be expected based on the prevalence of JIA. This study demonstrated that siblings of probands with JIA have an 11.6-fold increase in the risk of JIA (range 4.9–27.5, $p < 2.6 \times 10^{-8}$) compared to the general population [13]. Similarly, first cousins have a 5.8-fold increase in the prevalence of JIA (range 2.5–13.8, $p < 6.07 \times 10^{-5}$) compared to the general population. These observations also support a role for genetic factors in the predisposition to JIA.

In addition to clustering of JIA in some families, there is also evidence for familial autoimmunity in JIA. A case–control study of 110 families of probands with JIA and 45 healthy control families demonstrated that the prevalence of autoimmunity was three fold higher among relatives of JIA probands [14]. Of the 110 families of JIA probands, 81 families had at least one relative with a history of an autoimmune disorder, compared with only 15 of 45 families of control probands (OR 5.6 [2.5–12.7], $p < 4 \times 10^{-6}$). The prevalence of autoimmunity was higher among first degree relatives compared to second degree relatives. Thyroid autoimmunity was the most prevalent. In all, 52.3% of the relatives of the JIA probands were women, compared with 50.6% of the relatives of the controls. However, when those with autoimmune disorders were compared, 80.6% of the relatives of JIA patients and 80.0% of the relatives of controls were women. This is consistent with the female preponderance of autoimmunity. A follow up study demonstrated that the prevalence of autoimmunity was significantly higher among maternal aunts and maternal grandmothers compared to paternal aunts and paternal grandmothers, suggesting a maternal parent of origin effect in JIA [15]. These findings support the hypothesis that clinically distinct autoimmune phenotypes share common genetic susceptibility factors. The successful identification of variants that predispose to multiple autoimmune disorders, such as *STAT4* and *PTPN22,* strongly supports this hypothesis. This was the basis for the success of the ImmunoChip consortium in the identification of shared susceptibility variants across many autoimmune phenotypes.

3. JIA categories

Genetic studies for JIA are complicated by the heterogeneity of the condition. There are seven categories of JIA as defined by International League of Associations for Rheumatology (ILAR) classification criteria [16]. By definition, all patients with JIA have a chronic arthropathy with symptoms beginning at <16 years of age, however each category of JIA varies in its clinical symptoms and associated laboratory studies [16]. Systemic-onset JIA is characterized by fever and rash in addition to arthritis; polyarticular JIA is characterized by arthritis in five or more joints in the first six months of disease, and can be rheumatoid factor (RF)-negative or RF-positive. Polyarticular RF-positive JIA is phenotypically similar to rheumatoid arthritis (RA) in adults. Oligoarticular JIA is characterized by arthritis involving one to four joints in the first six months of disease. In many genetic studies, subjects with polyarticular RF-negative JIA and oligoarticular JIA are grouped together since these categories of JIA are phenotypically similar with the exception of the number of joints involved, thus suggesting that they may have a similar genetic basis. Additionally, the ILAR classification of JIA includes enthesitis-related arthritis (ERA), psoriatic arthritis, and unclassified arthritis. While the various JIA categories are characterized by different clinical features, natural histories, and immunogenetic associations, they all share in common chronic inflammation of the synovium.

Over the past two decades there have been numerous studies which have identified potential susceptibility loci for JIA. In some cases these studies have included subjects with all JIA categories, and in others they have included subjects limited to particular JIA categories. Oligoarticular and polyarticular RF-negative categories of JIA have been the most often investigated for genetic associations. Identified polymorphisms also vary by ethnic groups. A variety of techniques have been employed to identify potential variants including candidate gene studies of single nucleotide polymorphisms (SNP) and genome wide association studies (GWAS) including the use of high density genotyping arrays such as Immunochip. In this review we will describe the known HLA and non-HLA susceptibility loci for specific subtypes of JIA including oligoarticular JIA/polyarticular RF-negative JIA, polyarticular RF-positive JIA, systemic JIA, ERA and psoriatic JIA.

4. Genetics of oligoarticular JIA/polyarticular RF-negative JIA

Oligoarticular JIA is the most common category of JIA, affecting up to 40% of all patients with JIA. Patients with oligoarticular JIA have 4 or fewer joints affected during the first six months of the disease. After 6 months following onset, if the arthritis is confined to 4 or fewer joints, the disease is referred to as “persistent” oligoarticular JIA, whereas when more than 4 joints are involved, it is referred to as “extended” oligoarticular JIA [16]. Oligoarticular JIA has its peak incidence between 2 and 4 years of age and it has a female/male ratio of 3:1. One of its distinctions from other forms of arthritis is that it is associated with asymptomatic chronic anterior uveitis, a form of inflammatory eye disease which is more common in patients who are anti-nuclear antibody (ANA) positive. Like oligoarticular JIA, polyarticular RF-negative JIA also tends to predominantly affect girls, and has an early age of onset. Children with polyarticular RF-negative JIA are frequently ANA positive and they have an increased risk of chronic anterior uveitis. Thus, these two categories of JIA, which account for ~70% of all JIA cases, are phenotypically similar with the exception in the number of joints involved, and the symmetric involvement typically noted in polyarticular RF-negative JIA.

Please cite this article in press as: A.O. Hersh, S. Prahalad, Immunogenetics of juvenile idiopathic arthritis: A comprehensive review, Journal of Autoimmunity (2015), http://dx.doi.org/10.1016/j.jaut.2015.08.002