Juvenile Idiopathic Arthritis

Subjects: Others

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1. Introduction

Juvenile idiopathic arthritis (JIA) is a common type of chronic rheumatic diseases affecting children with the age of onset under 16 years, and an important cause of disability. Epidemiological studies showed that incidence rate of JIA ranges from 1.6 to 23 per 100,000 children annually and the prevalence of JIA was about 3.8–400 per 100,000 children in Europe[1]. Girls exhibit a higher incidence rate than boys (10.0/100,000 compared to 5.7/100,000)[1]. Its negative effects on children's physical development, as well as psychiatric development, cause serious damage to the quality of life of affected children, causing pain of active joints, physical disability, anxiety, and depression. There is no cure for JIA. JIA needs aggressive treatment to control its symptoms. For this difficult disease, it is important to understand the underlying molecular mechanisms of the development of JIA systematically through unbiased approaches. In recent years, people have started to gain knowledge about the multiomics architecture of JIA, thanks to the advance of high-throughput omics technologies.

2. JIA as a Heterogeneous Group of Diseases

JIA is a group of diseases, highly heterogeneous in terms of etiology and clinical presentation. It is classified into seven subtypes according to the Pediatric Task Force of the International League of Associations for Rheumatology (ILAR)[2], including systemic arthritis, oligoarthritis, polyarthritis RF-negative, polyarthritis RF-positive, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis[2]. In terms of the seven subtypes of JIA, oligoarthritis is the largest category of JIA, accounting for 50–60% of all cases; the other subtypes' frequencies are, polyarthritis (30–35%), systemic JIA (10–20%), psoriatic arthritis (2–15%), enthesitis-related arthritis (1–7%)[3]. After 25 years since the clinical application of the ILAR classification, it is understood, to date, that some subtypes of JIA are highly heterogeneous, e.g., the polyarthritis RF-negative and psoriatic subtypes[4]. Ambiguity in classifying certain patients has also been an issue. Clinical efforts are currently being made to revise the ILAR classification[5]. The advance of high-throughput omics technologies in recent years has gained us significant knowledge about the molecular mechanisms of JIA.

2.1. Systemic JIA (sJIA)

Systemic JIA (sJIA) is defined as fever and arthritis that last for 2 weeks or more, with one or more of the following features: (1) transient erythema, (2) lymphadenopathy, (3) hepatomegaly or splenomegaly, and (4) serositis[6]. However, sJIA is often difficult to diagnose because its symptoms are nonspecific, and highly similar to other inflammatory diseases[7]. Due to the significant similarity with adult Still's disease, it seems correct to regard sJIA as juvenile onset Still's disease[4]. As a typical autoinflammatory disease, sJIA is considered as a polygenic disease as adult Still's disease [8], rather than a monogenic disease. Although commonly with fever and joint symptoms, almost all autoinflammatory diseases with a monogenic etiology, such as TNF receptor-associated periodic fever syndrome and juvenile sarcoidosis/Blau syndrome, have a narrowly defined spontaneous feature and systemic inflammation[9].

2.2. Oligoarthritis and Polyarthritis

The JIA subtypes, oligoarthritis and polyarthritis, are differentiated only by the number of affected joints. Oligoarthritis affects four or fewer joints during the first 6 months after the onset of the disease. The oligoarticular subtype of JIA is further divided into two subtypes: persistent oligoarthritis and extended oligoarthritis. For the former, the number of joints involved is limited to four or less during the whole disease process, while for the latter, the number of joints involved is more than four after 6 months of onset. Compared to oligoarthritis, polyarthritis affects five or more joints in the first 6

months of disease onset. According to the presence or absence of rheumatoid factor (RF), it is further divided into subtypes of RF positive and RF negative[6]. There are a lot of features in common between oligoarticular and polyarticular JIA, such as relatively good reactivity and benign prognosis[10].

2.3. Psoriatic Arthritis

Psoriatic arthritis is characterized by typical psoriatic rash or strong family history (first-degree relative)[2].

2.4. Enthesitis-Related JIA

Enthesitis-related JIA is defined as an arthritis or inflammation of the attachment point of tendons or ligaments, with at least two of the following symptoms: (1) sacroiliac tenderness or inflammatory lumbosacral and spinal pain, not limited to cervical; (2) HLA-B27 positive; (3) male children with symptoms older than eight years of age. (4) HLA-B27 related diseases in first degree relatives in family history[2][6].

Undifferentiated arthritis, i.e., JIA patients cannot be assigned to one of the above JIA subtypes or can be assigned to more than one JIA subtype[2].

3. Research Progress

JIA is a group of diseases, highly heterogeneous in terms of etiology and clinical presentation. New molecular knowledge on different JIA subtypes encourages us to reconsider the JIA classification, but also highlights novel therapeutic targets to develop a cure for the devastating JIA. Multiomics studies make significant contribution to the understanding of the genetic basis and molecular mechanism of JIA pathogenesis. Similar to other complex human diseases, only a small proportion of JIA familial cases can be attributable to single-gene mutations. For the majority of sporadic JIA cases, the development of the disease is shaped by genetic, epigenetic elements, and environmental factors. Though JIA was classified into seven subtypes, phenotypic overlap was observed between subtypes, suggesting shared genetic/epigenetic basis. The relative low prevalence of JIA makes it hard to acquire enough samples to carry out GWAS on each individual subtype. Proper statistical methods for meta-analysis are needed to identify genetic loci shared by JIA subtypes by taking into account of pleotropic effects and potentially different effect directions between subtypes, as well as small sample sizes. In addition to genetic components, epigenetic modifications also contribute to JIA pathogenesis and development. The shared and distinct epigenetic regulations between JIA subtypes are even less understood, and the interactions between genetic and epigenetic mechanisms warrant further investigation. Integrative analyses of genetic, epigenetic, and transcriptome data are needed to elucidate the full picture of underlying molecular mechanisms of JIA subtypes and to classify JIA cases by molecular markers, and to further facilitate drug development and drug repositioning.

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