HLA AND JUVENILE IDIOPATHIC ARTHRITIS: AN OVERVIEW

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Abstract

Juvenile Idiopathic Arthritis (JIA) is an umbrella term referring to a group of disorders characterized by chronic arthritis and is the most common chronic rheumatic illness. Although the exact etiology of JIA remains unclear, it seems to be a complex genetic trait involving the effects of multiple genes related to immunity and inflammation. This review aims to throw light on the association between several HLA loci with JIA. HLA-B27 has consistently been found to contribute risk for pauciarticular JIA. HLA-DR1 and –DR4 are known to increase the risk for polyarticular JIA. Interestingly, HLA-DR4 might be protective in patients with Early Onset Pauciarticular Arthritis (EOPA). One of the unique features of JIA is that there appears to be a window of susceptibility during which children with predisposing HLA alleles or combination of alleles are maximally susceptible to the development of JIA, suggesting gene-gene and gene-environment interaction. To date no specific mechanisms have been identified as to how these genes are involved in disease induction. An alternative hypothesis is that the HLA molecules themselves undergo antigen processing and become immunogenic when presented by the other HLA molecule. Despite of complex traits underlying the different forms of JIA, it is assumed that the immune responses directed towards the self-antigens are the main clinical manifestations. However, genome wide studies are suggested for the identification of ‘novel’ transcripts of relevance to the disease and to enable the development of more appropriate intervention methods.

Key words: Juvenile Idiopathic arthritis, Rheumatoid arthritis, Etiology, HLA.

INTRODUCTION

Rheumatologists have a long term knowledge of the similarities and differences that the common chronic arthropathies of childhood share with the adult onset of Rheumatoid arthritis (Prahalad and Glass, 2002). Arthritis in children is more heterogenous than RA. The pathophysiological features including the genetic markers are different in many aspects from the adult counterparts, although the overall gross similarities are documented (Prahalad and Glass, 2002).

JIA is the most common chronic rheumatic illness and is a significant cause of short and long term disability (Weiss and Ilowite, 2005). It may be defined as persistent arthritis in one or more joints for at least 6 weeks if certain exclusionary conditions are eliminated; the disease onset subtype is defined by clinical symptoms in the first 6 months of the disease. Thus, classification is made at 6 months after diagnosis into one of the eight disease categories, each of which has it’s own specific characteristics, exclusions and descriptors (Thomson and Donn, 2002). JIA affects between 8 and 150 of every 100,000 children, depending on the analysis. Of these children, 50 percent are pauciarticular JIA, 40

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percent are polyarticular and 10 percent are systemic JIA.

Symptoms of JIA are often non-specific initially, and include lethargy, reduced physical activity, and poor appetite. The first manifestation, particularly in young children, may be limping. Children may also become quite ill, presenting with flu-like symptoms that persist (Schanberg et al., 2003). The cardinal clinical feature is persistent swelling of the affected joint(s), which commonly include the knee, ankle, wrist and small joints of the hands and feet. Swelling may be difficult to detect clinically, especially for joints such as those of the spine, sacroiliac joints, shoulder, hip and jaw, where imaging techniques such as ultrasound or MRI are very useful.

Pain is an important feature of JIA, but young children may have difficulty in communicating this symptom. Morning stiffness that improves later in the day is a common feature. Late effects of arthritis include joint contracture (stiff, bent joint) and joint damage. Children with JIA vary in the degree to which they are affected by particular symptoms (Schanberg et al., 2003).

The classification of inflammatory arthritis provide us some clues regarding the nature of these diseases (Prahalad and Glass, 2002). The American college of Rheumatology (ACR) uses the term ‘Juvenile Rheumatoid Arthritis’ (JRA) as the criteria of the classification which includes JRA of pauciarticular, polyarticular and systemic onset. On the other hand, the Europian League against Rheumatism (EULAR) uses the term ‘Juvenile Chronic Arthritis’ (JCA) which include not only the other three subtypes but also juvenile ankylosing spondylitis, psoriatic arthritis and arthritis associated with inflammatory bowel disease. The more recent International League of Associations for Rheumatology (ILAR) classified ‘Juvenile Idiopathic Arthritis’ (JIA) as seven subsets, including the spondyloarthropathies. The differences between the schemata are shown in Table I (Weiss and Ilowite, 2005). This article uses the ILAR system when applicable.

The very fact of the presence of subtypes in each and every classification system is sufficient to infer that juvenile arthritis is not a single entity with uniform clinical, laboratory and immunogenetic

**Table I:** Summary of the differences among the schemata (Weiss and Ilowite, 2005).

<table>
<thead>
<tr>
<th></th>
<th>ACR</th>
<th>EULAR</th>
<th>ILAR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset types</strong></td>
<td>3</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td><strong>Age of onset</strong></td>
<td>&lt;16 years</td>
<td>&lt;16 years</td>
<td>&lt;16 years</td>
</tr>
<tr>
<td><strong>Duration of arthritis</strong></td>
<td>&gt;6 weeks</td>
<td>&gt;3 months</td>
<td>&gt;6 weeks</td>
</tr>
<tr>
<td><strong>Includes JAS, JpsA</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Includes IBD</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Includes course</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviations: IBD-Inflammatory bowel disease; JAS-juvenile ankyslosing spondylitis; JpsA- juvenile psoriatic arthritis.
features, whereas RA in adults appear to be a single disease with different manifestations. On the contrary, patients with one subtype of JIA clearly differ from patients with the other subtypes. There are however similarities between some types of JRA/JIA and adult RA (Brewer et al., 1977). The similarities and the differences between JIA and RA are listed in Table II (Prahalad and Glass, 2002).

**Table II:** Similarities and differences between RA and JRA/JIA (Prahalad and Glass, 2002).

<table>
<thead>
<tr>
<th>Feature</th>
<th>RA</th>
<th>JRA/JIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classification criteria</td>
<td>Single disease with different</td>
<td>Phenotypically and genetically distinct</td>
</tr>
<tr>
<td></td>
<td>manifestations</td>
<td>subtypes</td>
</tr>
<tr>
<td>Gender</td>
<td>Females&gt;males</td>
<td>Females&gt;males except in systemic arthritis</td>
</tr>
<tr>
<td>Age of onset</td>
<td>Puberty plus; peak 4th to 5th decade</td>
<td>Polyarticular: throughout childhood; peak 1-3 years of age Pauciarticular: early childhood; peak 1-2 years of age Systemic: throughout childhood; no peak</td>
</tr>
<tr>
<td>Extended multiplex families</td>
<td>Present</td>
<td>Very rare</td>
</tr>
<tr>
<td>Family history of other</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>autoimmune disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical ocular involvement</td>
<td>Keratoconjunctivitis sicca</td>
<td>Chronic anterior uveitis</td>
</tr>
<tr>
<td>Prevalence</td>
<td>10/1000</td>
<td>0.86/1000</td>
</tr>
<tr>
<td>Ethnic distribution</td>
<td>Reported in all populations</td>
<td>EOPA is rare in non-caucasians</td>
</tr>
<tr>
<td>HLA association</td>
<td>HLA DRB1*0401,0404, 0101 in Caucasians</td>
<td>EOPA: HLA-A2,-DR5, -DR8, -DPB1*0201 (HLA-DR4 is protective) Late pauciarticular: HLA-B27 Polyarticular: HLA-DR1, -DR4</td>
</tr>
<tr>
<td>Shared epitope</td>
<td>Defined; amino acid positions 67-74 of third hypervariable region</td>
<td>Not described</td>
</tr>
<tr>
<td>Growth/developmental issues</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Th-1 mediated disease</td>
<td>Th-1 mediated disease (Pauciarticular: Also TH-2 mediated)</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>IgM RF common</td>
<td>IgM RF rare</td>
</tr>
<tr>
<td>Natural History</td>
<td>Majority have long term disability</td>
<td>Fewer than half have long term disability</td>
</tr>
</tbody>
</table>

EOPA, Early onset pauciarticular arthritis; HLA, human leukocyte antigen; JIA, juvenile idiopathic arthritis; JRA, juvenile rheumatoid arthritis; RA, rheumatoid arthritis; RF, rheumatoid factor; Th, T helper cells.
POSSIBLE ETILOGICAL FACTORS

The exact etiology of JIA remains unclear. However JIA seems to be a complex genetic trait involving the effects of multiple genes related to immunity and inflammation. Some hypothesize that arthritis may be triggered in a genetically predisposed individual by psychologic stress, abnormal hormone levels, trauma to a joint, even bacterial or viral infection. Several studies have implicated rubella and parvovirus B19 as possible causes of JIA because rubella virus persists in lymphocytes and establishes a focus of persistent infection in the synovium resulting in chronic inflammation (Lang and Shore, 1990). However these data remained difficult to replicate in other laboratories. Highly conserved bacterial heat shock proteins (HSK) may also act as potential disease triggers (Tucker, 1993). It is evident that JIA is more common in young girls and also common in Caucasians.

Various sources such as twin studies, family studies or association studies may provide evidences for a genetic component to the disease. Recent data from USA and Finland, however, suggest that the genetic contribution to JIA may be quite considerable. In the National Institute of Arthritis and Musculoskeletal and Skin Diseases, U.S.A. initial analysis of 71 affected sibling pairs showed that 63% were concordant for gender and 76% for onset type (Moroldo et al., 1997). This study was also the first to provide an estimate of the sibling recurrence risk (ɛs) for JIA of 15, although this is likely to vary between subgroups. Such a high ɛs is indicative of a factor shared between siblings – genetic or environmental. In another study of 118 affected sibling pairs, 14 pairs of twins were identified in which both twins have arthritis. One pair comprises a girl with polyarthritis and a boy with persistent oligoarthritis. The other 13 pairs (11 monozygotic, 2 dizygotic and 2 of unknown zygosity) were concordant for gender (nine female, four male), disease onset and disease course (Prahalad et al., 2000).

A study conducted in Finland on 41 JIA multicase families with 88 affected siblings over a period of 15 years estimated the ɛs of JIA to be near 20 (Saila et al., 2000). Within this set of families there were eight sets of monozygotic twins, two of which were concordant for JIA. Both sets of twins were concordant for disease course but were unexpectedly different for disease onset (Savolainen et al., 2000). A concordance rate of 25% for a disease with a population prevalence of 1 per 1000 implies a relative risk of 250 for a monozygotic twin. These data taken together provide convincing evidence that there is a substantial genetic component to JIA.

THE ROLE OF HLA

The most extensively studied susceptibility locus for autoimmune disorders is the Major Histocompatibility complex (MHC) located on chromosome 6p (Figure 1) (Mehra and Kaur, 2003). This region is densely packed with more than 200 genes most of which are highly essential to the immune system, including the human leukocyte antigen (HLA) genes. The genes of the MHC in general, and the HLA genes in particular, are highly polymorphic.

Much of the genetic works undertaken in the past three decades centered round HLA genes. These earlier studies of HLA and JIA included children classified according to either the EULAR or the ACR criteria. Studies have consistently shown associations between HLA and several autoimmune diseases, including both RA and JIA. HLA associations are distinct for RA and JIA, demonstrating that the immunogenetic factors involved in susceptibility to these two diseases are indeed different. Numerous studies of associations of JIA with both HLA class I and class II genes have been described, with the class I associations being consistently more limited than those for class II.

The earliest reported association was with an MHC class I gene, HLA-B27 in older children with pauciarticular disease (Haas et al., 1994). This has been followed by associations of HLA with most types of JIA, although in varying degrees of strength, some reflecting similarities to adult arthropathies and others are unique to childhood.
However the different clinical subtypes of JIA themselves differ in their HLA associations. For instance, the class I gene HLA-B27 has consistently been found to contribute risk for pauciarticular JIA, especially among older males. HLA-DR1 and -DR4, class II genes, have been reported to increase the risk for polyarticular JIA. Much as in adults with RA, HLA-DR4 is associated with RF-positive polyarticular disease in older children. Interestingly, this gene might be protective in patients with EOPA. In this subtype, combined class I and II MHC associations are seen. Other MHC-encoded genes such as LMP7 have also been shown to be associated with early-onset JIA (Prahald et al., 2001). HLA-A2, HLA-DR5, HLADR8 and HLA-DPB1*0201 have all been shown to be associated with JIA by several investigators, and interactions between these alleles yield high odds ratios for EOPA (Brunner et al., 1993; Nepom and Glass, 1992; Paul et al., 1993; Paul et al., 1995; Ploski et al., 1995; Van Kerckhove et al., 1990). It is possible that in this type of JIA, four individual genes (one HLA-A gene, two HLA-DR or DQ genes and an HLA-DP gene) may be involved. Confirming the associations that have been reported, linkage between pauciarticular JIA and the HLA region have been shown both by using transmission disequilibrium testing in simplex families (Moroldo et al., 1997) and by allele sharing among affected sibling pairs (Prahald et al., 2000). Similarly, linkage between polyarticular JIA and the HLA region has also been shown by allele sharing among affected sibling pairs (Prahald et al., 2000).

One of the unique features of JIA is that there appears to be a window of susceptibility, during which children with predisposing HLA alleles or

**Figure 1.** Gene map of the human leukocyte antigen (HLA) region. The HLA region spans 4 × 106 nucleotides on chromosome 6p21.1 to p21.3, with class II, class III and class I genes located from the centromeric (Cen) to the telomeric (Tel) end. HLA class I molecules restrict CD8+ cytotoxic T lymphocyte function and mediate immune responses against ‘endogenous’ antigens and virally infected targets, whereas HLA class II molecules are involved in the presentation of ‘exogenous’ antigens to T helper cells. The HLA class III region contains many genes encoding proteins that are unrelated to cell-mediated immunity but that nevertheless modulate or regulate immune responses in some way, including tumour necrosis factor (TNF), heat shock proteins (Hsps) and complement proteins (C2, C4). (Adapted from Mehra and Kaur, 2003).
combination of alleles are maximally susceptible to the development of JIA, suggesting gene–gene and gene–environment interactions (Murray et al., 1997).

In a study of 680 patients with JIA and 254 ethnically matched, unrelated controls, survival analysis was performed to calculate the age by which 50% and 80% of children with particular HLA alleles and combinations of alleles develop disease. Certain alleles were strongly associated with early susceptibility to pauciarticular JIA, including HLA-A2, -DR8, -DR5 and -DPB1*0201. Of the children carrying at least one of these alleles, 50% had disease onset before their third birthday. Among children who carry HLA-A2 and any two HLA-DR alleles (HLA-DR3, -DR5, -DR6, -DR8), the median age at onset of pauciarticular disease was only 2.7 years. Combinations of HLA-A2 and -DPB1*0201 and one DR allele narrowed the window further to a median age at onset of 2.4 years. Gender strongly influenced the age at which many of the alleles have their effect. These results demonstrated the complex interactions between different HLA susceptibility alleles that influence the age of onset of JIA.

In a study with 521 caucasians JIA patients and 537 controls, it has been found that 2 HLA-DRB1 alleles ( DRB*08 and *11) were associated with increased risk and 2 with decreased risk (DRB1*04 and *07) of JIA. Their phenotypic frequencies also differed between subgroups. HLA-DRB1*04 although negatively associated for other subgroups was found to be associated with an increased risk for RF-positive polyarthritis. Some alleles at the HLA-DQA1 locus were associated with increased risk (DQA1*0103, *04 and *05) and others decreased risk ( DQA1*02 and *03) of JIA. The associations at individual loci are reflected in the haplotype associations seen. Three haplotypes namely DRB1*08-DQA1*0401-DQB1*0402; DRB1*11-DQA1*05-DQB1*03; and DRB1*1301-DQA1*01-DQB1*06 were associated with the increased risk and one, DRB1*04-DQA1*03-DQB1*03, with the decreased risk of JIA as a whole as shown in Table III.

Table III: Odds ratios associated with the possession of HLA haplotypes in JIA subjects versus controls (Thomson et al., 2002).

<table>
<thead>
<tr>
<th>DRB1- DQA1- DQB1 haplotype</th>
<th>All JIA</th>
<th>Systemic</th>
<th>Persistent oligoarticular</th>
<th>Extended Oligo</th>
<th>Poly RF-negative</th>
<th>Poly RF-positive</th>
<th>Enthesitis</th>
<th>Psoriatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>01-0101-0501</td>
<td>1.5(0.9,2.4)</td>
<td>1.2(0.5,2.5)</td>
<td>1.2(0.6,2.2)</td>
<td>1.9(1.3,3.5)</td>
<td>0.8(0.4,1.9)</td>
<td>1.0(0.3,3.3)</td>
<td>4.9(2.1,12.1)</td>
<td>3.8(1.7,5.9)</td>
</tr>
<tr>
<td>0404-0303</td>
<td>0.6(0.4,0.9)</td>
<td>0.7(0.3,1.3)</td>
<td>0.4(0.2,0.7)</td>
<td>0.1(0.0,3)</td>
<td>0.7(0.4,1.4)</td>
<td>3.9(1.5,9.9)</td>
<td>1.5(0.6,3.7)</td>
<td>0.4(0.1,1.1)</td>
</tr>
<tr>
<td>11-05-03</td>
<td>2.1(1.1,3.9)</td>
<td>4.3(1.9,9.5)</td>
<td>2.2(1.0,4.7)</td>
<td>3.0(1.3,6.8)</td>
<td>1.6(0.6,4)</td>
<td>1.2(0.3,4.5)</td>
<td>0.7(0.2,3.4)</td>
<td>0.9(0.2,3.5)</td>
</tr>
<tr>
<td>13-01-06</td>
<td>3.0(1.0,8.5)</td>
<td>1.7(0.4,7.7)</td>
<td>6.4(2.1,19.7)</td>
<td>1.5(0.3,3.7)</td>
<td>1.7(0.4,7.7)</td>
<td>1.3(0.1,11.9)</td>
<td>1(1.1)</td>
<td>4.5(1.1,19.2)</td>
</tr>
<tr>
<td>0701-0201-0201</td>
<td>0.7(0.4,1.2)</td>
<td>0.6(0.3,1.6)</td>
<td>0.2(0.1,0.7)</td>
<td>1.3(0.6,2.8)</td>
<td>0.7(0.3,1.8)</td>
<td>0.2(0.1,7)</td>
<td>0.7(0.2,2.5)</td>
<td>1.3(0.7,4.7)</td>
</tr>
<tr>
<td>0801-0401-0401</td>
<td>4.1(1.7,9.7)</td>
<td>2.3(0.7,7.5)</td>
<td>6.1(2.4,15.8)</td>
<td>10.3(3.9,27.4)</td>
<td>2.3(0.7,7.5)</td>
<td>0.6(0.1,7.3)</td>
<td>0.8(0.1,6.9)</td>
<td>2.9(0.8,11.2)</td>
</tr>
</tbody>
</table>

Results are only shown for haplotypes where there are evidence for a difference between JIA subgroups or overall association. Odds ratios significantly different from 1 at the 5% level are shown in bold.
To date, no specific mechanisms have been identified as to how these genes are involved in disease induction. In addition there is some debate as to the relative importance of the closely linked HLA-DR and HLA-DQ loci (Haas et al., 1995). In support of this, one study has demonstrated a polymorphism in the Y box of the DQ promoter region associated with pauciarticular onset JIA (Haas et al., 1994). Another group has demonstrated limited linkage disequilibrium between the early onset pauciarticular JCA associated locus HLA-DPB1*0201 and certain DQ/DR alleles, further highlighting the difficulties of identifying the true disease related gene (Davies et al., 1994). Given the normal function of HLA molecules in presenting processed antigenic peptides (both foreign and self) to effector T lymphocytes, as part of an immune or inflammatory reaction, it has been speculated that particular HLA risk alleles present potentially arthritogenic peptides to such T cells. An alternative hypothesis is that the HLA molecules themselves undergo antigen processing and become immunogenic when presented by other HLA molecule. This may explain in part how multiple independent HLA disease related alleles commonly exist in one patient. The nature of the peptides presented by the HLA molecules on antigen presenting cells in JIA patients draw great interest. This may provide clues as to the pathogens involved especially if extrinsic antigens can be identified which may mimic the self antigens (Albani, 1994). Although their specific role in immunopathogenesis has yet to be elucidated, it is clear that the ‘at risk’ HLA haplotypes influence disease outcome. For example, an HLA DR1 haplotype predicts a poor outcome with respect to arthritis in the pauciarticular onset group, but protects from eye disease, whereas the presence of HLA DR5 predicts more eye disease (Giannini et al., 1991). In a similar manner a genetic polymorphism of the proteasomal subunit LMP2 (a non-HLA gene encoded in the MHC region on chromosome 6) has been associated with late onset pauciarticular JCA (B27 associated), especially those with more severe disease (Pryhuber et al., 1996).

At a nearby locus, also within the MHC region, a polymorphism in the TAP2 gene which encodes for a transporter associated with antigen processing (TAP2B), is associated with early onset pauciarticular JIA (Giannini et al., 1991). Both of these findings may implicate antigen processing either at a qualitative or quantitative level in disease susceptibility.

In conclusion, it is evident that complex traits underlie the different forms of JIA, each one probably unique. Despite such differences, immune responses directed towards self antigens are likely to be central to the pathogenesis of each type of disease. This responsiveness is determined by the particular array of genes present in an individual. Specific HLA allele may favour the presentation of one peptide antigen over another to a specific T cell repertoire predetermined genetically at the thymic level and modified by the presence of null alleles in particular TCR families. HLA association in JIA may help to define more homogenous groups of patients, but identifying other genetic risk factors may lead to better definition of JIA subgroups and hence clarification of the HLA associations.

Although there are similarities between the inflammatory arthritis occurring in adults and children, RA and JIA appear to be distinct phenotypically, except for the older child with RF-positive polyarticular arthritis. Furthermore, the various subtypes of JIA appear to be distinct entities and could represent different diseases with distinct etiological and genetic factors. Paradoxically, clinically distinct autoimmune disorders do appear to share common genetic susceptibility factors. In this context, it is plausible that there are common genetic susceptibility factors that predispose an individual to an autoimmune disorder, with other genetic (especially HLA) and/or environmental factors that determine the type of specific disorder and its manifestations.

The idea of identifying ‘novel’ transcripts of relevance to disease would become attractive. Microarray based expression technology would be useful if the correct sample materials are available, such as paired blood and synovial fluids. This would
allow to look at alterations in mRNA levels as an indication of gene activation or regulation. This type of work, however, requires samples before and after the treatment which may not always be ethically acceptable when studying disease in children. The majority of the genetic research conducted for JIA so far were retrospective in nature. This may identify genes involved in disease susceptibility. Perhaps the more useful and clinically relevant genetic approach is to define genetic predictors of outcome or disease severity. This can be attempted by prospectively following a cohort of clinically well-defined patients. Again the issue of multiple samples becomes important and possibly limiting. Identifying, at initial presentation, patients who are most likely to have the more aggressive course of disease would have substantial implications for treatment interventions. For the understanding of JIA genetics to progress, international collaborations that maximize the resource potential would appear to be the way forward. This would allow larger-scale association and linkage studies to be carried out. Coupled with the rapid advances in genomic and proteomic technologies, these studies may pave the way forward to a better understanding of this complex genetic disease. Accurate outcome data are also essential to achieve the ultimate aims of being able to predict outcome and establish new therapies for children with JIA.

Thus the advent of more comprehensive approaches allowing genome-wide studies have become essential. The use of peptide libraries to look for relevant antigens and the further development of transgenic and gene knockout animal models are likely to herald greater understanding of the complex genetic traits and environmental triggers underlying the different forms of JIA. This, in turn, will enhance the prospect of developing more specific, effective and potentially curative treatments for these diseases. However expertise should be the baseline of care of children with JIA, as early appropriate treatment is essential to ensure best possible short and long term outcome for children with JIA (Sawhney, 2002.).

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