CHAPTER - 1

INTRODUCTION
**Introduction**

Juvenile idiopathic arthritis (JIA) is a diverse group of diseases characterized by constant arthritis with start before age of 16 years (Ravelli and Martini, 2007). 50% of them carry on having active disease throughout adulthood. As the word idiopathic suggests, the pathogenesis of JIA is still unknown but some previous observations suggests role of genetic and environmental factors in the establishment of disease.

JIA includes seven mutually exclusive categories: systemic arthritis (SoJIA), oligoarticular (oligoJIA), polyarticular rheumatoid factor negative (poly-JIA RF-), polyarticular rheumatoid factor positive (poly-JIA RF+), enthesitis-related arthritis (JIA-ERA), psoriatic arthritis (PsA), and undifferentiated arthritis (UnA). Oligoarthritis is divided into 2 sub categories: persistent and extended (Petty et al., 2004). Different inclusion and exclusion criteria have been designed for each of these categories. Arthritis in one or more joints along with quotidian fever of at least 2 weeks duration is known as SoJIA. Presence of 1-4 affected joints in first six months of disease with absence of fever is known as Oligoarthritis. Polyarthritis, which may be rheumatoid factor positive or negative, involves five or more joints. Patients with psoriasis and HLA-B27 positivity are excluded from these 3 categories. Psoriatic arthritis involves presence of both arthritis and psoriasis.

Enthesitis related arthritis (ERA) is the most prevalent category in India and in other parts of Asia (Aggarwal et al., 2004; Kunjir et al., 2010). Disease onset in boys older than 6 years of age with arthritis, enthesitis and family history of HLA-B27 related diseases is defined as ERA category of JIA. It has strong similarity with adult spondyloarthropathies i.e ankylosing spondylitis (AS) in several characteristics, such
as occurrence of enthesitis, inflammatory back pain and anterior uveitis, and presence of a strong family history. Almost 30-40% of children with JIA-ERA develop ankylosing spondylitis after 10 years of disease (Petty RE et al., 2001; Kunjir et al., 2010).

Major histocompatibility complex (MHC) Class I molecule, Human Leukocyte Antigen (HLA) B27 allele likely plays a role in binding and presenting antigenic peptides to T cells. Due to its unusual cell biology and novel homodimeric structures, HLA-B27 is suspected to play a pathogenic role in JIA-ERA (Kollnberger et al., 2009). 80% Indian and 60-70% Caucasian JIA-ERA children show strong association with HLA- B27, similar to ankylosing spondylitis (AS) patients (Kunjir et al., 2010; Aggarwal et al., 2012; Thomson et al., 2002; Berntson et al., 2008).

HLA-B27 has marked genetic polymorphism, as is true for several other HLA class I molecules, nucleotide sequence variations in exons 2 and 3 encoding the alpha 1 and alpha 2 domains of antigen-binding cleft of the HLA-B27 molecule accounts for this variability (Khan, 2010). Currently, 105 subtypes of HLA-B27 are known (Khan, 2013). Association of AS with B27 subtypes has been studied in various populations around the world. Some subtypes, such as B*27:02, B*27:04, B*27:05, B*27:07 and B*27:08, confer particularly high susceptibility to AS. In the Caucasian population, the common subtypes associated with AS are HLA-B*27:05, whereas, Mediterranean population has HLA-B*27:02 subtype and Chinese have HLA-B*27:04 (Khan, 2010; Liu X et al., 2010). HLA-B*27:04 confers a greater risk of AS than HLA-B*27:05 in the Chinese population, (Liu X et al., 2010; Liu Y et al., 2010) B*27:06 another HLA-B27 subtype differs, in only two amino acids from B*27:04 and is reported to be negatively or weakly associated with AS (Hou TY et al., 2007).
Limited data is available on the relationship of various HLA-B27 subtypes with susceptibility to JIA-ERA. In a Latvian study, 55% of 25 children with JIA-ERA had B*27:05 (Stanevicha et al., 2010) However, no significant difference in the distribution of B27 subtypes found between patients with juvenile-onset and adult-onset AS in southern Chinese population (Mou Y et al., 2010).

We propose to study the prevalence of common HLA-B27 subtypes in children with JIA-ERA and adult AS and see if there is any genotype-phenotype association as there is no data available on HLA-B27 subtypes in children with JIA-ERA and the data on HLA-B27 subtypes in AS is also very limited from our country.

Prevalence of various HLA-B27 subtypes in JIA-ERA will be compared to that in adult ankylosing spondylitis (AS) to see if certain subtypes lead to disease expression in childhood. In addition we will also look at the distribution of JIA sub groups in North Indian population and prevalence of HLA-B27 in these groups.

Thus the objectives of study are:

A. Prevalence of HLA-B27 in children with JIA-ERA and other JIA categories

B. Prevalence of HLA-B27 subtypes in B27 positive children with JIA-ERA

   a. Study the genotype phenotype correlation of HLA-B27 subtypes

   b. Compare the prevalence of HLA-B27 subtypes in JIA-ERA and adult ankylosing spondylitis (AS).