



**Karolinska  
Institutet**

Institutionen för Medicin Solna, Enheten för Lungmedicin och  
Institutionen för Klinisk Forskning och Utbildning, Södersjukhuset

# Studies of Different Clinical Manifestations of Sarcoidosis and the Role of Genetic Factors

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska  
Institutet offentligen försvaras på svenska språket i Thoraxaulan,  
N2:U1, Karolinska Universitetssjukhuset Solna.

**Fredagen den 6 december, 2013, kl 09.00**

av

**Pernilla Darlington**

ST-läkare i lungmedicin

*Huvudhandledare:*

Professor Johan Grunewald  
Karolinska Institutet  
Institutionen för Medicin Solna  
Enheten för Lungmedicin

*Bihandledare:*

Professor Anders Eklund  
Karolinska Institutet  
Institutionen för Medicin Solna  
Enheten för Lungmedicin

Med dr Michael Runold  
Karolinska Institutet  
Institutionen för Medicin Solna  
Enheten för Lungmedicin

*Fakultetsopponent:*

Professor Anders Blomberg  
Umeå Universitet  
Institutionen för Folkhälsa  
och klinisk medicin  
Enheten för Medicin

*Betygsnämnd:*

Docent Mikael Adner  
Karolinska Institutet  
Institutionen för Miljömedicin  
Enh f Experimentell astma & allergiforskning

Professor Anders Bucht  
Umeå Universitet  
Institutionen för Folkhälsa  
och klinisk medicin  
Enheten för Medicin

Professor Eva Lindberg  
Uppsala Universitet  
Institutionen för Medicinska vetenskaper  
Enheten för Lungmedicin och allergi

**Stockholm 2013**

## ABSTRACT

Sarcoidosis is a systemic disease of unknown etiology characterized by the formation of non-necrotizing granulomas in the affected organs. Engagement of the lungs and/or thoracic lymph nodes (LN) are found in more than 90 % of all cases, but almost any organ such as the eyes, skin, heart and nervous system can be involved. Genetic factors influence the risk for disease as well as the clinical picture seen in sarcoidosis and especially the genes localized to the human leukocyte antigen (HLA) region on chromosome six are believed to be of importance. For example, the HLA-DRB1\*0301 allele is found to be strongly associated with Löfgren's syndrome (LS). Characteristic for LS is an acute onset usually with fever, bilateral ankle arthritis and/or erythema nodosum and bilateral hilar lymphadenopathy with in some cases parenchymal infiltrates. The HLA-DRB1\*0301 allele is also associated with an accumulation of T cells expressing the T cell receptor variable gene segment AV2S3 in bronchoalveolar lavage fluid (BALF) of sarcoidosis patients.

The aim of this thesis has been to identify risk factors for different clinical manifestations in sarcoidosis as well as markers of importance for the inflammatory cell response seen in sarcoidosis.

The results show that HLA-DRB1\*04 positive sarcoidosis patients had an increased risk for the three organ engagements associated with Heerfordt's syndrome. Heerfordt's syndrome is a phenotype of sarcoidosis that in its complete form consists of uveitis, parotid and/or salivary gland enlargement and cranial nerve palsy.

In comparison to BALF where a high CD4/CD8-ratio is strongly associated with sarcoidosis, the CD4/CD8-ratio in the affected LNs of sarcoidosis patients had no diagnostic value. Further, in HLA-DRB1\*03 positive patients the associated accumulation of AV2S3+ T cells was strictly compartmentalized in BALF. This finding indicates an airborne antigen as the triggering factor in sarcoidosis.

The risk for cardiac sarcoidosis (CS) was significantly higher in patients with an abnormal electrocardiography (ECG) compared to those with a normal ECG. The risk for CS was highest in patients who had a pathologic ECG in combination with cardiac related symptoms. Further, non-LS was associated with an increased risk for CS.

In LS patients was the absence of HLA-DRB1\*03 a risk factor for extra-pulmonary manifestations (erythema nodosum and ankle arthritis excluded). Another risk marker in all patients was HLA-DRB1\*04/\*15 where half of the patients had extra-pulmonary manifestations.

In conclusion, the HLA-DRB1\*04 allele is associated with an increased risk for involvement of the eyes, parotid and/or salivary glands and cranial nerves in sarcoidosis patients. Moreover, an increased CD4/CD8-ratio in enlarged LNs is not diagnostic for sarcoidosis in comparison to BALF where a high ratio is strongly associated with sarcoidosis. Further, a pathologic ECG is a risk marker for CS in sarcoidosis patients. Finally, not only the single HLA-DRB1 alleles are of importance for the risk of extra-pulmonary manifestations in sarcoidosis, but also the allele combinations and where especially the combination HLA-DRB1\*04/\*15 calls for an increased awareness and a more intensive follow-up.