

# Genetics of Sarcoidosis Workshop

## Sponsoring IC: NHLBI, NIAID, ORD

### EXECUTIVE SUMMARY

**Purpose/Objective:** To review the studies conducted in the last 10 years in sarcoidosis genetics and define short and long term scientific goals.

Sarcoidosis is a systemic granulomatous disease which can affect multiple organs, with the most common being the lungs, eyes, and skin. The pathological hallmark of the disease is the characteristic noncaseating multinucleated granuloma. In the severe form of the disease, granuloma expansion and/or persistence can lead to fibrosis and loss of organ function. Estimates of the numbers of Americans afflicted with this disease range from 13,000 to 134,000. In the United States (U.S.); between 2,600 and 27,000 new cases are diagnosed each year.

A genetic predisposition to sarcoidosis is indicated by observations of familial clustering, increased concordance in monozygotic twins over other siblings, and variations in susceptibility and disease presentation among different ethnic groups. Genetic studies in sarcoidosis have gone through three phases – candidate gene studies, affected sib pair (ASP) linkage analysis and most recently, genome wide association studies (GWAS). These phases have been largely driven by sampling convenience, available genotyping technology and statistical methodology. While investigators have failed to identify a specific genetic signature for sarcoidosis, numerous studies have identified genetic associations with specific ethnic groups and disease subtypes. Based on these initial studies, the genetic contribution to sarcoidosis is likely to involve many genes each with modest effect, which in order to be identified will likely require the analysis of large samples consisting of diverse phenotypes and ethnic make up.

A major focus of discussion at the workshop was the lack of uniform clinical phenotypes in sarcoidosis (i.e., phenotypes that everybody can agree upon) among referral centers and individual investigators. Earlier population-based studies, which had been focused more on accurate histopathological diagnoses than comprehensive phenotype, family characteristics, ethnicity, and environmental factors, were discussed. The constitution of a very large registry of sarcoidosis patients that would include detailed phenotypic information was proposed. This would markedly facilitate genetic studies.

Interesting results have been contributed to the field of sarcoidosis genetics by various European groups which have analyzed clusters of patients with different ethnicity compared to the one analyzed in the US; recently, the first genome wide association study (GWAS) conducted in a German population, has identified a strong genetic association between the disease and Annexin A11, a gene with complex and essential functions in several biological pathways, including cell apoptosis and proliferation.

#### **Recommendations:**

- Launch a community based genetics study of sarcoidosis that will utilize a web-based approach and include information from patients and their physicians. This could be used in the US and other countries. The patients should enter the system at diagnosis and have follow-up questions that incorporate outcome with or without therapy. The registry

could have many open-ended questions spanning personal history, familial history, and environmental exposure information so the maximum amount of data can be collected, and elements may emerge that will help to re-define sarcoidosis sub-phenotypes. Furthermore, utilizing a community-based approach, the registry could capture patients that are referred to subspecialties other than pulmonary medicine. Through collaborations with support group- and faith-based organizations, the registry should reach a larger number of minorities, which are disproportionately affected by the disease. If successful, this could be a model for community based studies of genetics of other diseases.

- The registry of phenotypic information should also, in time, become a biorepository of biological material to be shared among interested investigators, and which will provide the substrate to design genetic studies.
- A recommendation endorsed by all participants to the workshop called for a stronger collaboration with the scientific community in Europe and around the world that include sharing technologies, phenotypic information, and biological samples.
- An NHLBI funded study: ACCESS (A Case Control Etiological Study of Sarcoidosis) has collected between 1995 and 2002 approximately 1,400 DNA samples from well phenotyped sarcoidosis patients and matched controls; the samples are stored in the NHLBI biorepository. The meeting participants recommended that this samples and the data set that accompany them, should be examined for quality and, if found suitable, a preliminary GWAS study could be conducted. These existing DNA samples should be used for initial discovery of potential genetic risk factors of Sarcoidosis. The findings (a small set of SNPs) should be replicated in another (may be bigger) population, such as the community based genetics study of sarcoidosis proposed above.

A final recommendation was to promote studies to identify relevant gene networks and pathways important in sarcoidosis, which may prove more informative than studies that focus on single candidate genes.

The meeting was held in Bethesda on July 25, 2008 in Bethesda, Maryland.

### **Workshop participants**

Chair: Gary Hunninghake M.D., Ph.D., Iowa City;

Robert P. Baughman, M.D., Cincinnati; Andrew Fontenot, M.D., Denver; Sylvia Hoffman, Germany; Michael Iannuzzi, M.D., Syracuse; Lisa A. Maier, M.D., Denver; David R. Moller, M.D., Baltimore; Benjamin A. Rybicki, Ph.D., Detroit; Henry Yeager, Jr. M.D., Washington, DC;

NIH staff: Sandra Colombini-Hatch, M.D., NHLBI; Dorothy B. Gail, Ph.D., NHLBI; Weiniu Gan, Ph.D., NHLBI; James P. Kiley, Ph.D., NHLBI; Tony Punturieri, M.D., Ph.D., NHLBI; Richard T. Sawyer, Ph.D., NIAID. Herbert Y. Reynolds, M.D., NHLBI;