GENE POLYMORPHISMS IN FIBROTIC SARCOIDOSIS

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Sarcoidosis is a systemic disease of unknown cause, which is characterized by the presence of noncaseating granulomas in one or multiple organs. In approximately 90 percent of patients with sarcoidosis, the disease is manifested as pulmonary granulomas. Although parenchymal abnormalities often resolve spontaneously, about 20-25% of cases will ultimately develop pulmonary fibrosis. Fibrosis of the lung parenchyma is associated with poor pulmonary function and a bleak prognosis with increased morbidity and mortality.

Fibrosis is characterized by a disproportionate increase in extracellular matrix (ECM) proteins. The exuberant ECM production is believed to originate from an imbalance between cytokines involved in tissue healing and remodelling. Sarcoidosis is likely to be a genetically complex disease that involves a combination of genetic loci (polygenic) conferring disease predilection or phenotypic variation of disease manifestation. Single nucleotide polymorphisms (SNP's) in genes that encode for components involved in tissue injury and repair may influence the risk of developing pulmonary fibrosis in sarcoidosis. The effects of genetic variation on sarcoidosis phenotypes may appear as changes of such parameters as radiography, lung function or serum levels of the disease marker.

The results described in this thesis strongly support the influence of genetic variation on the disease parameters that are used to describe the phenotypes of pulmonary sarcoidosis. These parameters include disease marker levels in serum, evolution of chest X-ray, and lung function data. The results show that a number of SNP’s can add to the propensity to develop pulmonary fibrosis as seen for TGF-β3

polymorphisms in relation to radiographic evolution, or that a combination of SNP's on one allele (haplotypes) may predict the odds of developing chronic sarcoidosis and fibrosis in males. Gene polymorphisms in genes of disease markers ACE, KL-6 and YKL-40 inform us about their influence on protein functionality. The identification or evaluation of polymorphisms in genes that encode proteins which are or may be used as sarcoidosis disease markers clearly underline the relevance of considering gene polymorphisms in an attempt to identify normal and deviating levels of disease markers.

For the clinician, however, having to account for the genetic variation of a disease marker may be cumbersome. Means to circumvent the potentially expansive number of reference intervals that are based on e.g. gender, age, length, and gene polymorphisms can be accomplished by formulating a simple algorithm that accounts for any variable known to influence the measures of a marker. As illustrated in this thesis, the Z-score offers a useful way to apply genetically-specific marker levels in practice. In order to grasp the genetic influence on the vast and complex pathways which lead to pulmonary fibrosis in sarcoidosis, the expansion of useful fibrosis parameters are needed to be able to give the affected individual a proper risk assessment and a fitting treatment regimen. The associations described in this thesis will hopefully prompt future investigations into the delineation of the functional roles of polymorphisms in genes that are involved in the pathogenesis of pulmonary fibrosis in sarcoidosis.