Sjögren's Quarterly
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Why Language Matters

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Historically, Sjögren's has been classified into 'primary' and 'secondary' disease. 'Primary' Sjögren's is defined as a standalone entity occurring in the absence of another systemic autoimmune disease, whereas 'secondary' disease is associated with the presence of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) or systemic sclerosis (SSc), for example. Notably, the presence of a coexistent autoimmune disease is very common in Sjögren's (approximately 30% overall), when organ specific autoimmunity is also included.

In our recently published article (Kollert & Fisher, *Rheumatology*) we reviewed the historical justification for the distinction of 'primary' and 'secondary' Sjögren's based on genetics, clinical presentation, chronology, histology and serology, and found it difficult to justify the dichotomy based on exisiting evidence. We therefore recommend further research, and advocate abandoning the term 'secondary' unless strong evidence emerges of a pathological difference between these subsets. We further argue for a nomenclature including the associated disease (Sjögren's in association with…) to not only emphasize the second autoimmune disease but also Sjögren's itself. In our perspective, Sjögren's is an underresearched disorder, a situation that is even worse for patients with so called 'secondary' disease. This stands in sharp contrast to the potential impact of Sjögren's on quality of life, even when compared to other systemic rheumatological disorders. Accordingly, it has been shown in a study analyzing patients with rheumatoid arthritis, systemic sclerosis, lupus and Sjögren's, that patients with Sjögren's have the lowest levels in certain domains of quality of life (vitality, social function) and the second lowest levels after systemic sclerosis in all investigated quality of life scores. Moreover, patient-reported symptoms are stronger predictors of quality of life as compared to systemic manifestations in Sjögren's, illustrating

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Dr. Christopher Lessard Receives 3.7 Million Dollar Grant from NIAMS to Continue Sjögren's Research

Christopher Lessard, PhD, of the Oklahoma Medical Research Foundation (OMRF), was recently awarded a five-year grant with a $3.7 million-dollar budget from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), a part of the National Institutes of Health, to continue his ongoing efforts to understand how genetic variations lead to Sjögren's disease.

Dr. Lessard coordinates the OMRF-led Sjögren's Genetics Network (SGENE), a collaboration of more than 26 international research groups dedicated to understanding the genetics of Sjögren's. To date, SGENE researchers have collected and analyzed DNA samples from

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the high importance of these symptoms for all Sjögren's patients including those with other systemic autoimmune diseases.

'Secondary' can also imply a temporal aspect suggesting that Sjögren's often manifests after the associated autoimmune disease. However, the literature clearly shows that Sjögren's comes first in a considerable proportion of patients, which speaks against a chronological basis for the historical terminology. Although we found no convincing evidence for a difference in phenotype between 'secondary' and 'primary' Sjögren's, going beyond obvious differences caused by an overlap with the associated disease, we did find some suggestions that the clinical phenotype of the associated disease may sometimes differ. It is conceivable that these differences may relate to an interaction between the pathophysiology of Sjögren's and that of the associated disease. For example, patients with rheumatoid arthritis and Sjögren's exhibit a more aggressive rheumatoid arthritis phenotype including more bone erosions. For lupus, it has been shown that patients with concomitant Sjögren's responded better to a B cell-targeted therapy (epratuzumab) than patients with lupus alone. This might be due to more pronounced B cell activity in these patients, which might also underlie the observation that rheumatoid arthritis patients with Sjögren's have higher disease activity. It can be hypothesized that rheumatoid arthritis patients with Sjögren's might respond better to treatment modalities targeting B cells and maybe even interferon (e.g. rituximab, JAK inhibitors), which warrants study.

Patients with 'secondary' Sjögren's are often excluded from clinical trials and were not incorporated in the development of the most recent classification criteria for Sjögren's. They were considered in the widely used 2002 criteria but neither histopathology nor autoantibodies were necessary for classification as 'secondary' Sjögren's. Thus, recent clinical trials investigating new compounds for patients with Sjögren's typically recruit patients with primary Sjögren's only. So it seems unclear if a drug which is eventually proven to have efficacy for these 'primary' Sjögren's patients; will be accessible to patients with 'secondary' disease also. Conversely, studies of other systemic autoimmune diseases such as lupus or rheumatoid arthritis have typically not excluded patients with concomitant Sjögren's. This provides a largely unexplored opportunity to derive additional early signals of potential efficacy in Sjögren's. Even in the absence of salivary gland biopsy, anti-Ro positive patients meeting the 2016 ACR/EULAR criteria recruited in large clinical trial programs targeting rheumatoid arthritis, lupus and systemic sclerosis, could have assessment of patient reported outcomes for dryness alongside unstimulated salivary flow. Many such patients have been treated with novel agents in the past and we may have missed multiple opportunities to generate evidence to support a drug-specific mode of action in Sjögren's, or to investigate Sjögren's as a potential stratification for treatment response in the investigated disease.

Admittedly, there are often pragmatic and understandable reasons for focusing research on 'primary' disease, in order to have a more homogenous cohort and reduce the presence of confounding factors. However 'secondary'

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disease, when feasible, should not be neglected. Further research should seek to either establish the similarity between Sjögren's in the presence or absence of another systemic autommue disease when meeting the same classification criteria, or else provide a stronger justification than currently exists for this historic distinction. This will also avoid the risk that patients with 'secondary' disease are unnecessarily excluded from novel treatments arising from current development programs. In some situations inclusion/exclusion criteria for clinical trials could be adjusted to allow recruitment of 'secondary' patients. However this would require careful consideration of classification, drug mechanism, trial objectives and trial outcome measures. At one end, a drug targeting glandular disease with salivary flow as outcome may have no reason to exclude patients with another systemic autoimmune disease, whereas at the other end, assessment of systemic disease might be complicated by the presence of other diseases. However, polyautoimmunity is very common in rheumatology, and we need to understand how best to apply our therapeutic options within this complex setting.

Taken together, as there is currently no evidence for a major difference between the phenotype of 'secondary' and 'primary' Sjögren's we argue in favor of using the same set of classification criteria for both. Moreover, we take the side of abandoning the term 'secondary' in favor of 'Sjögren's in association with' to emphasize not only Sjögren's but also the associated autoimmune disease. The overlap between different systemic autoimmune diseases should be regarded as an opportunity to foster drug development and to further stratify our available treatment modalities and to personalize our therapies. ■

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more than 3,000 Sjögren's patients, and have identified approximately 20 genes associated with increased risk of Sjögren's. "While these discoveries have significantly improved our understanding of the genetics, we suspect that this in only a small fraction of the genes associated with Sjögren's. In comparison, research on the related autoimmune diseases, systemic lupus erythematous and rheumatoid arthritis, have identified more than 100 associated genes," Lessard said.

Research supported by Dr. Lessard's new grant will leverage SGENE resources to recruit and analyze more than 10,000 DNA samples from Sjögren's patients around the world. Increasing the sample size will improve the discovery power of this study beyond that of any previously conducted genome wide association study in Sjögren's, thus promising the discovery of many additional genes. Any research groups who are interested in collaborating on this international initiative are encouraged to contact Dr. Lessard and his research team.

In addition to discovering new genes associated with Sjögren's, this grant will allow the research team to explore which variants in the DNA alter expression of specific genes in both peripheral blood cells and disease-relevant salivary gland tissue. "We now know that the non-protein-coding sequences that make up the majority of the human genome actually play an important role in regulating cell type-specific changes in gene expression. Since the majority of genetic variants associated with complex genetic diseases, like Sjögren's, are in those non-protein-coding regulatory part of the genome, these risk variants most likely influence disease by changing the expression of a gene or, potentially, several genes. Understanding how the genetic variants we identified in the genome-wide association study alter gene expression in circulating immune cells from the blood and different cell types in the salivary gland will provide important new insights into heritability of Sjögren's," said Lessard. By measuring the differences in gene expression between normal and disease tissues, and between disease tissues from patients with varying disease symptoms and severity, this award promises to provide new perspectives on the biological processes that drive the development and progression of Sjögren's. Further, Dr. Lessard and his research team at the OMRF are hopeful that their findings will provide important groundwork to improve the diagnostic strategies used to identify patients with increased risk for serious complications, and inform future therapeutic development. ■

A Note from the Foundation:

The Sjögren's Foundation would like to congratulate Dr. Lessard, his research team, and the Oklahoma Medical Research Foundation on this new award.

Dr. Lessard has been studying Sjögren's at the OMRF since 2007. As a past recipient of a Sjögren's Foundation research grant, we are thrilled that Dr. Lessard has continued to make notable strides to improve the Sjögren's community's understanding of this complex disease.