Bicaudal D2 is a novel autoantibody target in systemic sclerosis that shares a key epitope with CENP-A but has a distinct clinical phenotype

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A B S T R A C T

We studied the clinical correlations and epitopes of autoantibodies directed to a novel autoantigen, Bicaudal D2 (BICD2), in systemic sclerosis (SSc) and reviewed its relationship to centromere protein A (CENP-A). 451 SSc sera were tested for anti-BICD2 using a paramagnetic bead immunoassay and then univariate and multivariate logistic regression was used to study the association between anti-BICD2 and demographic and clinical parameters as well as other SSc-related autoantibodies. Epitope mapping was performed on solid phase matrices. 25.7% (116/451) SSc sera were anti-BICD2 positive, of which 19.0% had single specificity anti-BICD2 and 81.0% had other autoantibodies, notably anti-CENP (83/94; 88.3%). Compared to anti-BICD2 negative subjects (335/451), SSc sera had significantly lower mean percent skin thickness (0.84±0.79 vs. 1.09±0.79, p = .004) and interstitial lung disease (ILD; 52.4% vs. 29.0%, p = .024). Epitope mapping revealed a serine- and proline-rich nonapeptide SPSPGSSLP comprising amino acids 606–614 of BICD2, shared with CENP-A but not CENP-B. We observed that autoantibodies to BICD2 represent a new biomarker as they were detected in patients without other SSc-specific autoantibodies and were the second most common autoantibody identified in

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Autoantibodies directed against intracellular autoantigens, such as anti-nuclear antibodies (ANA) are biomarkers used for the diagnosis and estimating the prognosis of systemic sclerosis (SSc) [1-3]. SSc-specific autoantibodies are also components of SSc classification criteria, are of value in predicting disease onset, identifying meaningful clinical subsets, and some are purported to have a pathogenic role [reviewed in [3-5]]. The spectrum of autoantibodies in SSc is wide but the most common include those directed to centromere proteins A and B (CENP-A, -B), Ro52/TRIM21, topoisomerase I (topo-I or Scl-70) and RNA polymerase III (RNAPIII) [1,2,6]. Despite tremendous progress in identifying autoantibody targets in SSc, 2-10% of SSc sera with a positive ANA had no detectable autoantibodies to SSc-related autoantigens and 6-15% of SSc sera were reported as having a negative ANA on conventional indirect immunofluorescence (IIF) assays [7,8]. Accordingly, unique and clinically-important autoantibodies remain to be detected.

A recent abstract identified human protein Bicaudal D homolog 2 (BICD2) as a novel, specific, intracellular target of SSc autoantibodies [9]. In that study of SSc and other systemic autoimmune rheumatic diseases (SARD), the prevalence of anti-BICD2 in SSc sera was 32% as compared to 4.2% in controls (odds ratio, OR = 8.7) [9]. The goals of our study were to determine the demographic, clinical and serological characteristics of SSc patients with anti-BICD2 in an unselected cohort of SSc patients and to identify the epitope(s) bound by anti-BICD2 antibodies.

1. Introduction
Autoantibodies directed against intracellular autoantigens, such as anti-nuclear antibodies (ANA) are biomarkers used for the diagnosis and estimating the prognosis of systemic sclerosis (SSc) [1-3]. SSc-specific autoantibodies are also components of SSc classification criteria, are of value in predicting disease onset, identifying meaningful clinical subsets, and some are purported to have a pathogenic role [reviewed in [3-5]]. The spectrum of autoantibodies in SSc is wide but the most common include those directed to centromere proteins A and B (CENP-A, -B), Ro52/TRIM21, topoisomerase I (topo-I or Scl-70) and RNA polymerase III (RNAPIII) [1,2,6]. Despite tremendous progress in identifying autoantibody targets in SSc, 2-10% of SSc sera with a positive ANA had no detectable autoantibodies to SSc-related autoantigens and 6-15% of SSc sera were reported as having a negative ANA on conventional indirect immunofluorescence (IIF) assays [7,8]. Accordingly, unique and clinically-important autoantibodies remain to be detected.

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2. Materials and methods

2.1. Ethical considerations

This study was conducted in compliance with The Code of Ethics of the World Medical Association (Helsinki Declaration) for experiments involving humans; Uniform Requirements for manuscripts submitted to biomedical journals. Ethics committee approval for this study was obtained at McGill University (Montreal, Canada) and at all participating study sites. All subjects provided informed written consent to participate.

2.2. Design

Cross-sectional, multicenter study of 451 subjects from the Canadian Scleroderma Research Group (CSRG) cohort with study visits between September 2004 and January 2016 (described below).

2.3. Study subjects

Adult SSc subjects in the CSRG cohort were recruited by rheumatologists across Canada. Approximately 98% of subjects enrolled in the CSRG registry fulfilled the 2013 ACR/EULAR classification criteria for SSc [10]. Four hundred and fifty-one SSc sera were evaluated, as well as 99 systemic lupus erythematosus (SLE), 30 autoimmune inflammatory myopathy (AIM), 100 infectious disease (ID), 150 non-connective tissue diseases (non-CTD: sera referred for neurological disease autoantibody testing), and 34 healthy individuals (HI) were used as control and comparator samples in the anti-BICD2 immunoassay described in 2.1.4 (Fig. 1).

2.4. Serology

Using standard operating procedures, serum was collected and sent to a central laboratory (Mitogen Advanced Diagnostics Laboratory, University of Calgary) where aliquots were stored at −80°C until needed. ANA’s were detected by indirect immunofluorescence (IIF) on Hep-2 substrate (Hep-2000; ImmunoConcepts, Sacramento, CA, USA) and read on a Zeiss Universal microscope fitted with a 150 W ultraviolet light source by technologists with >10 years of experience. The terminology used for pattern descriptions followed the recent International Consensus on ANA Patterns (ICAP) [11]: https://www.anapattems.org/trees.phpAutoantibodies against CENP-A and/or CENP-B, topo-I, RNAPIII, PM/Scl (PM75 and/or PM100), Ro52/TRIM21, platelet derived growth factor receptor (PDGFR), Ku, Th/To, NRR80/hUFB (human up-stream binding factor), and fibrillinin (USRNP) were detected by a line immunoassay (Euroline Systemic Sclerosis Profile: Euroimmun, Luebeck, Germany), and anti-Jo-1 and U1-RNP were detected by