A Bioinformatics Analysis Reveals Novel Pathogens as Molecular Mimicry Triggers of Systemic Sclerosis

Athanasios Gkoutzourelas, Maria Barmakoudi, Dimitrios P. Bogdanos

Mediterr J Rheumatol 2020;31(1):50-70
A Bioinformatics Analysis Reveals Novel Pathogens as Molecular Mimicry Triggers of Systemic Sclerosis

Athanassios Gkoutzourelas, Maria Barmakoudi, Dimitrios P Bogdanos
Department of Rheumatology and Clinical Immunology, Faculty of Medicine, University of Thessaly, Larissa, Greece

ABSTRACT

A recent bioinformatic analysis revealing dominant B cell epitopes of systemic sclerosis-specific autoantibodies, including anti-centromere B, anti-topoisomerase I and anti-fibrillarin, has demonstrated the existence of several in silico antigenic mimics of pathogens that could act as triggers of the respective dominant autoepitopes. Based on those findings, the aim of the present study was to use a more comprehensive bioinformatic analysis. We demonstrated the presence of a plethora of novel microbial mimics, unnoticed by the studies so far conducted, which share remarkable amino acid similarities with the respective autoantigenic epitopes. This bioinformatic approach coupled by in vitro testing of the homologous self/non-self-mimics in serum samples from patients with systemic sclerosis may provide novel evidence of immunological cross-reactivity, implicating currently ignored or overlooked pathogens, which may indeed play a role in the induction of SSc-specific autoantibodies and assist efforts to understand the pathogenesis of this enigmatic disease.

Mediterr J Rheumatol 2020;31(1):50-70
https://doi.org/10.31138/mjr.31.1.50
Article Submitted: 28 Nov 2019; Revised Form: 1 Feb 2020; Article Accepted: 17 Feb 2020; Published: 31 Mar 2020

Keywords: autoantibody, autoimmunity, autoimmune rheumatic diseases, infection, molecular mimicry

Corresponding Author:
Dimitrios P. Bogdanos, MD, PhD
Associate Professor of Medicine and Autoimmune Diseases
Director and Chairman, Department of Rheumatology and Clinical Immunology
Faculty of Medicine, School of Health Sciences, University of Thessaly
Viopolis, Mezourlo
Larissa 40500, Greece
Tel.: +30 2413502880
Fax: +30 2413501016
E-Mail: bogdanos@med.uth.gr
Website: www.autorheumatology.com

ABBREVIATIONS:
aa: Amino acid
Ab: Antibody
AutoAb: Autoantibody
ARD: Autoimmune rheumatic diseases
SjS: Sjögren’s syndrome
SLE: Systemic lupus erythematosus
SSc: Systemic sclerosis

Cite this article as: Gkoutzourelas A, Barmakoudi M, Bogdanos DP. A Bioinformatics Analysis Reveals Novel Pathogens as Molecular Mimicry Triggers of Systemic Sclerosis. Mediterr J Rheumatol 2020;31(1):50-70.
MOLECULAR MIMICRY IN SYSTEMIC SCLEROSIS

INTRODUCTION

Molecular mimicry has been proposed as a pathogenic mechanism for an autoimmune disease’s development, as well as a probe useful in uncovering its aetiologic agents. The concept of molecular mimicry is based on the abundant epidemiological, clinical, and experimental evidence of an association of infectious agents with specific autoimmune diseases, and observed immunological cross-reactivities between self-targets and microbial determinants. Immunological cross-reactivity is demonstrated when antibodies against a viral or microbial epitope (linear or conserved) can recognize a self-sequence of a known autoantigen, because of their antigenic similarity. In the case of linear epitopes, this similarity is likely to be a consequence of amino acid (aa) similarities between the core epitopic region of the respective self/non-self-epitopes. If this occurs, a cross-reactive immune response against the determinant shared by the host and the virus can evoke a tissue-specific immune response that is presumably capable of eliciting cell and tissue destruction. The probable mechanism is generation of autoantibodies or cytotoxic cross-reactive effector lymphocytes, that recognise specific determinants on target cells. By a complementary mechanism, the microbe can induce cellular injury and release self-antigens, which generate immune responses that cross-react with additional but distinct self-antigens, a mechanism which we have termed “multiple hit” molecular mimicry. However, the ultimate documentation of this mechanism has been elusive in humans. Presently, proof for molecular mimicry relies on the availability of structural data of viral and self-peptides that elicit cross-reactive immune responses and pathological features of the disease in experimental animal models.

The information derived from animal studies is of undoubted value, but experimental models of human disease suffer from severe limitations since they rarely reproduce the human condition faithfully. Thus, several of the mimics that have been able to induce experimental autoimmune disease do not ultimately relate to the human setting. Molecular mimicry studies conducted in human biomaterial are almost impossible to undertake because they necessitate access to biomaterial (sera, cells, tissue) before exposure to the pathogen; such material is rarely accessible for testing.

Several studies have implicated molecular mimicry as a likely mechanism responsible for the induction of systemic sclerosis (SSc)-specific autoantibodies. Sera from SSc patients recognize a sequence originated from human cytomegalovirus (CMV) late protein UL94 which appears to be homologous to the novel antigen-2 (NAG-2), which is expressed in endothelial cells. Anti-UL94 antibodies from SSc patients not only bind to NAG-2 on endothelial cells, but also can provoke apoptosis. This is rather intriguing, because when anti-UL94 CMV antibodies are bound to fibroblasts, they obtain a proliferative phenotype. Another similarity between UL70 protein shared with Topoisomerase I, a major autoantigen in SSc, has been reported as a likely triggering factor in this disease, but no evidence of cross-reactivity has so far been obtained. A recent paper by Gourh et al. has revisited this topic and investigated the relationships between disease-related auto-antibodies, their respective autoantigens/autoepitopes, and genetic HLA associations, which confer susceptibility to geographically/ethnic distinct SSc cohorts. Through their meticulous analysis, and the application of bioinformatics tools, these investigators recognized viral-obtained peptidyl sequences from the Mimiviridae and Phycodnaviridae families, which are highly homologous to their SSc-specific autoantigenic counterparts, and could theoretically act as inducers of the disease via immunological cross-reactivity and molecular mimicry. Going through their identified viral sequences, it became apparent to us that the number of reported mimics was relatively smaller than what we thought we could obtain. We therefore decided to comprehensively assess the extent of self/non-self-mimicry and to provide a complete list of likely mimics also using a bioinformatics approach.

MATERIAL AND METHODS

Basic Local Alignment Search Tool Protein (BLASTp), BLASTp2 (National Center for Biotechnology Information, NCBI, National Library of Medicine, Bethesda, MD, USA) (https://blast.ncbi.nlm.nih.gov/Blast.cgi?PAGE=Proteins) and Proteininfo (Rockefeller University, New York, NY, USA) (http://prowl.rockefeller.edu/prowl/proteininfo.html) computer-assisted programmes were used for aa comparisons and identification of peptidyl sequences homologues to those used as reference sequences reported by Gourh et al. “RQRAVALYFIDKLAL”, from the immunodominant topoisomerase I epitope and “LQEAAEFLVHLFED” from the centromere A (CENPA) epitope. The (BLASTp) is a sequence comparison algorithm, enables comparison of a protein or peptide sequence with a database of sequences and identifies similar and potentially homologous sequences. The comparison of sequences is based on substitution matrices (such as BLOSUM62 that is used by BLAST by default) that score alignments of evolutionarily divergent protein sequences. We performed our BLASTp analyses as per Gourh et al. with slight modifications. When necessary, confirmatory Proteininfo analyses were performed, as we previously described.

The Ethics Committee of the University General Hospital of Larissa, Greece granted an approval for the completion of the study in the University of Thessaly. Statistical analyses for the significance of the observed similarities were automatically obtained by the acquisition of aligned sequences via BLASTp search engines.
RESULTS
Taking advantage of the work performed by Gourh et al., who determined the immunodominant human topoisomerase I epitope, CENPA fibrillarin and its microbial mimics, we expanded this work emphasizing key elements that have gone unnoticed. First, we explored homology between the bioinformatically predicted immunodominant peptide sequences and microbial protein sequences to assess whether the mimics we identified by BLASTp analysis differ to those reported by Gourh et al. (Figure 1 and 2, Suppl. Tables 1-3). In addition to that, we performed a Proteininfo analysis using 5meric sequences originated from topoisomerase I epitope “RQRAVALYFIDKLAL,” and CENPA sequence “LGEAAEFLVHLFED,” and requested for identical epitope “RQRAVALYFIDKLAL,” and CENPA sequence addition to that, we performed a Proteininfo analysis by Gourh et al. (18), who determined the immunodominant human topoisomerase I (Scl70) protein sequences to assess whether the mimicries we observed score or higher than that are expected to occur by chance in a database search, and is a measure of the significance of homology. Some of the alignments produced by BLAST could be due to chance and not due to a biologically meaningful relationship between the two sequences. These alignments would have a high E-value. In contrast, alignments with low E-values are not random, and the two sequences might be related biologically. This is why Gourh et al. reported only high-scored matches with the E values of <0.05.

The Authors reported that the matched homologous peptides originated from the nucleocyttoplasmic large DNA virus clade viruses, in the Mimiviridae family. (19) We anticipated that analyses limited to matches with high quality matched, might lead to an underestimation of potential antigenic mimics for reasons we thoroughly explored in various species some of which differed from those recently published. (19) Gourh et al. reported only one sequence in topoisomerase I, “RQRAVALYFIDKLAL,” that had remarkable high-scored matches within the viral database at an Expected (E) value of <0.05. E-value represents the number of BLAST alignments with the observed score or higher than that are expected to occur by chance in a database search, and is a measure of the significance of homology. Some of the alignments produced by BLAST could be due to chance and not due to a biologically meaningful relationship between the two sequences. These alignments would have a high E-value. In contrast, alignments with low E-values are not random, and the two sequences might be related biologically. This is why Gourh et al. reported only high-scored matches with the E values of <0.05.

The Authors reported that the matched homologous peptides originated from the nucleocyttoplasmic large DNA virus clade viruses, in the Mimiviridae family. (19) We anticipated that analyses limited to matches with high quality matched, might lead to an underestimation of potential antigenic mimics for reasons we thoroughly explored in various species some of which differed from those recently published. (19) Gourh et al. reported only one sequence in topoisomerase I, “RQRAVALYFIDKLAL,” that had remarkable high-scored matches within the viral database at an Expected (E) value of <0.05. E-value represents the number of BLAST alignments with the observed score or higher than that are expected to occur by chance in a database search, and is a measure of the significance of homology. Some of the alignments produced by BLAST could be due to chance and not due to a biologically meaningful relationship between the two sequences. These alignments would have a high E-value. In contrast, alignments with low E-values are not random, and the two sequences might be related biologically. This is why Gourh et al. reported only high-scored matches with the E values of <0.05.

The Authors reported that the matched homologous peptides originated from the nucleocyttoplasmic large DNA virus clade viruses, in the Mimiviridae family. (19) We anticipated that analyses limited to matches with high quality matched, might lead to an underestimation of potential antigenic mimics for reasons we thoroughly explored in various species some of which differed from those recently published. (19) Gourh et al. reported only one sequence in topoisomerase I, “RQRAVALYFIDKLAL,” that had remarkable high-scored matches within the viral database at an Expected (E) value of <0.05. E-value represents the number of BLAST alignments with the observed score or higher than that are expected to occur by chance in a database search, and is a measure of the significance of homology. Some of the alignments produced by BLAST could be due to chance and not due to a biologically meaningful relationship between the two sequences. These alignments would have a high E-value. In contrast, alignments with low E-values are not random, and the two sequences might be related biologically. This is why Gourh et al. reported only high-scored matches with the E values of <0.05.

The Authors reported that the matched homologous peptides originated from the nucleocyttoplasmic large DNA virus clade viruses, in the Mimiviridae family. (19) We anticipated that analyses limited to matches with high quality matched, might lead to an underestimation of potential antigenic mimics for reasons we thoroughly explored in various species some of which differed from those recently published. (19) Gourh et al. reported only one sequence in topoisomerase I, “RQRAVALYFIDKLAL,” that had remarkable high-scored matches within the viral database at an Expected (E) value of <0.05. E-value represents the number of BLAST alignments with the observed score or higher than that are expected to occur by chance in a database search, and is a measure of the significance of homology. Some of the alignments produced by BLAST could be due to chance and not due to a biologically meaningful relationship between the two sequences. These alignments would have a high E-value. In contrast, alignments with low E-values are not random, and the two sequences might be related biologically. This is why Gourh et al. reported only high-scored matches with the E values of <0.05.

Table 1. Representative microbial and viral mimics of topoisomerase I (Scl70, Scl70) dominant autoepitope.

| Source             | Protein                          | E-value | Consecutive identity | Local E-value | Sequence       |
|--------------------|----------------------------------|---------|----------------------|---------------|----------------|
| Human              | Topoisomerase I                   |         |                      |               |                |
| Moumouvirus goulette | Topoisomerase I b                 | 0.064   | 73%                  | 6             | 3E-10          | R Q I A T A L Y F I D N F A L |
| Bodo saltans virus  | Topoisomerase I b                 | 0.064   | 91%                  | 9             | 3E-10          | A T A L Y F I D K L A       |
| Tupanivirus deep ocean | Topoisomerase I b                | 0.064   | 73%                  | 6             | 3E-10          | R Q I A T A L Y F I D N F A L |
| Faunusvirus sp.     | Topoisomerase I b                 | 0.73    | 90%                  | 6             | 2              | A L Y F I D E L A         |
| Prokaryotic DNA virus sp. | putative pepitidase                | 0.067   | 100%                 | 6             | 0.0000002      | Y F I D K L                |
| Egerthelaeus bacteria | asparagine synthase (glutamine-     | 1       | 91%                  | 11            | 3E-11          | A V A L Y F V D K L A     |
| Lactobacillus aviarius | amino acid permease               | 8.2     | 100%                 | 9             | 2E-10          | V A L Y F I D K L         |
| OM182 bacterium     | Glutamate synthase family protein | 12      | 90%                  | 8             | 4E-10          | A V A L Y F I D R L      |
| Gammaproteobacteria bacterium | Glutamate synthase e | 12 | 90% | 8 | 4E-10 | A V A L Y F I D R L |
| TMED134             | Family protein                    | 33      | 82%                  | 6             | 1              | A Y A L Y F I D Q L       |
| Bacteroides cacuminis | Glutaminase (glutamine-         |         |                      |               |                |

Figure 1. Representative microbial and viral mimics of topoisomerase I (Scl70, Scl70) dominant autoepitope.

For each sequence (i.e., the 15-mer of and the 15-mer of topoisomerase I), the first five-homology pairs with viruses and the first five-homology pairs with bacteria were chosen, according to the following criteria:
- The pairs ought to have at least 6 (≥6) consecutive homologous aa, allowing one aa difference, but of the same side chain group (i.e., I→V or Y→F)
- Only one pair was chosen from same species
- No pairs from phages were included
- No pairs from uncultured bacteria or viruses were included
- No hypothetical proteins were included
discuss. An extensive list of matches provided by our analysis in Suppl Tables 1 and 2. All results were included, independently of their E-value, except hypothetical proteins with high E-value and results with big gaps. No homologies found with human herpesviruses (including Epstein-Barr virus and human cytomegalovirus, which were blasted separately, as those viruses are very frequently involved in the induction of SSc-related autoimmunity), hepatitis C virus, Brucella species and Staphylococci, by selection. Homologies with eukaryotes have not been included, as in their great majority have to deal with conserved DNA topoisomerases from fish, arthropoda, etc.

**Figures 1 and 2** depict representative homologies, which we considered of interest, as typical examples of self/non-self-similarities at the level of >5-mer aa length overlaps.26

**DISCUSSION**

In the present study, we extended the understanding for the potential role played by molecular mimicry in the induction of SSc-specific autoimmunity. On the basis of a bioinformatics analysis, we provided an exhaustive list of microbial mimics of dominant B-cell autoantigenic epitopes, implying that several previously unnoticed pathogens may indeed play role in the development of autoreactive B cell responses related to SSc. This enormous number of pathogenic determinants shares remarkable aa homologies with two key autoepitopes, one originated from topoisomerase I (Scl70) and one from centromere A. Based on these findings, hypothesis-driven experiments working on the extent by which synthetic peptides spanning the respective aa sequences could be tested for antibody reactivity using sera from anti-centromere A and anti-Scl70 positive SSc patients. Such testing answers two key questions: first, how many of those peptides are targeted by cross-reactive antibodies? Ultimately, we could narrow down the list of biologically-meaningful peptides from few hundreds to a few dozens. Second, what is the relevance of the nature of the mimicking microbial peptides in relation to disease’s pathogenesis; ie, do these homologous peptides originate from pathogens which can infect humans, and to what extent?

The list of mimicking peptides is extensive, because...
it is well-known that homologies do not need to be remarkable in order to induce cross-reactivity; mimics restricted to 5-6-aa long, may have great success in immunological terms.26 For example, Kanduc et al.26 found that 34 pentameric sequences from the viral capsid protein of human papillomavirus shared sequences with human proteins that are associated with cardiovascular diseases. Trost et al. showed that all human proteins present bacterial motifs at the level of 5-, 6-, 7- and 8-mer aa.27,28 Thus, aa similarity or even antigenic mimicry (shared motifs between foreign and self-antigens) is not sufficient to establish a significant connection. If the mimics do not involve human proteins with biologic function such as enzymes or proteins with critical function, such targeting may embrace biologic meaningless, and must be disregarded. Foreign/human T-cell mimicry is more complicated, as motif sharing may involve very limited number of aa, and most molecular mimics cannot be identified by sequence alignment alone.9 Sharing of a 6-aa long peptide between hepatitis B virus DNA polymerase and myelin basic protein was enough to induce experimental encephalomyelitis in rabbits. In fact, databases currently exist, which provide open access to experimentally verified peptide sequences displaying molecular mimicry and immunological cross-reactivity, and can serve as sources of in vivo and in vitro research.29 For example, epidemiological studies, microbiological data and immunological evidence of mimicry currently support a link between ankylosing spondylitis, HLA B27, and bacterial infection.30 A single substitution of one aa is more than enough to abrogate such an effect, highlighting the importance of the shared motifs. Dozens of papers have been published so far (including those generated by our group), reporting the existence of such mimics that operate both at the B-cell (cross-reactive antibodies) and the T-cell level at various autoimmune diseases.4,8,20-23,31,32 We have also been able to show that mimicking alignments per se are not sufficient enough to reveal cross-reactive mimics.24,25,33 On the other hand, epitopic sequences, which do not share 100% identity, may well be able to act as cross-reactive targets of an antibody, if the dissimilar aa are not sufficient to change the antigenicity of the sort peptides. This is exemplified in particular at T-cell epitope mimics.5 Given the relatively limited number of previously observed similarities which involve SSc-specific autoantigens and pathogens, we hypothesized that BLAST search could identify more mimics, and therefore would uncover likely microbial and viral triggers of SSc autoantibodies. Such identification could provide a convincing theoretical explanation for non-self-triggered autoimmunity in SSc by the involvement of molecular (antigenic) mimicry and subsequent immunological cross-reaction. If the attack

Figure 3. Step-wise approaches used by approaches used by Gourh et al.19 and the current study.
of the pathogen is met by the formation of strong T- and B-cells responses, aiming at controlling or preventing the infiltration of the virus in cells and tissues, and if the immune system is equipped with the ‘wrong’ genetic background, which restricts such responses at epistolic level that accidentally share homologies with self-epitopes, a catalysis of reactions may happen which leads to autoimmunity and immune-mediated inflammation. Of particular interest was that we recognized several mimics that Gourh et al. did not identify, just because they could not fulfill their strict scoring criteria, which, by the way, are totally justifiable. With these results at hand, we speculate that local identical mimics must further be examined. Neither Gourh et al. nor we have experimentally tested the identified mimics. Immunological cross-reactivity can and must be defined through humoral and cellular studies involving synthetic peptides, which must be recognized by serum samples or T-cells from patients with SSc seropositive for their respective disease-specific autoantibodies. Only then, we can speculate on their potential pathogenic significance.

In conclusion, the present bioinformatics analysis allows the development of a hypothesis that is valid and can must be tested in vitro and in vivo. It also provides important clues as to whether molecular mimicry is a likely mechanism for the induction of autoimmunity related to SSc, and opens a window of opportunity for specifically designed research focusing on the similarities so far published.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

FINANCIAL SUPPORT
This research is co-financed by Greece and the European Union (European Social Fund - ESF) through the Operational Program «Human Resources Development, Education and Lifelong Learning 2014-2020» in the context of the project “The role of molecular mimicry in autoimmunity: systemic sclerosis as a model” (MIS 5006628).

ACKNOWLEDGEMENTS
We appreciate the assistance given by Mr. Georgios Efthymiou with parts of the bioinformatic analyses.

ETHICS STATEMENT
This study does not involve investigation of humans or animals.

REFERENCES
1. Bogdanos DP, Choudhuri K, Vergani D. Molecular mimicry and autoimmune liver disease: virtuous intentions, malign consequences. Liver 2001;21:225-32. [https://doi.org/10.1002/1520-0332(200101)21:1<225::AID-LIV4>3.0.CO;2-3] [PMID: 11454184]
2. Rojas M, Restrepo-Jimenez, P, Monsalve, DM, Pacheco, Y, Acosta-Ampudia, Y, Ramirez-Santana, C et al. Molecular mimicry and autoimmunity. J Autoimmun 2018;95:100-23. [https://doi.org/10.1016/j.jaut.2018.10.012] [PMID: 30509385]
3. Bogdanos DP, Gao B, Gershwin ME. Liver immunology. Compr Physiol 2013;3:567-98. [https://doi.org/10.1002/cphy.c120011] [PMID: 23720233] [PMCID: PMC4201126]
4. Oldstone MB. Molecular mimicry and immune-mediated disease. FASEB J 1999;12:1255-65. [https://doi.org/10.1096/fasebj.12.12.1255] [PMID: 9761770]
5. Wucherpfenng KW, Strominger JL. Molecular mimicry in T cell-mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein. Cell 1995;80:695-705. [https://doi.org/10.1016/0092-8674(95)90348-8] [PMID: 7534214]
6. Smyk DS, Rigopoulos EI, Bogdanos DP. Potential Roles for Infectious Agents in the Pathophysiology of Primary Biliary Cirrhosis: What’s New? Our Infect Dis Rep 2013;15:14-24. [https://doi.org/10.1016/s11908-012-0304-2] [PMID: 23188623]
7. Koutoumpas AL, Smyk DS, Bogdanos DP. Induced Experimental Model of Primary Biliary Cirrhosis: At Last. Int J Hepatol 2014;2014:843873. [https://doi.org/10.1155/2014/843873] [PMID: 25580001] [PMCID: PMC4280654]
8. Ehser J, Holdener M, Christen S, Bayer M, Pfleischkher JM, Hintermann E, et al. Molecular mimicry rather than identity breaks T-cell tolerance in the CYP2D6 mouse model for human autoimmune hepatitis. J Autoimmun 2013;42:39-49. [https://doi.org/10.1016/j.jaut.2012.11.001] [PMID: 23200317]
9. Bogdanos D, Pual T, Rust C, Vergani D, Beuers U. Primary biliary cirrhosis following Lactobacillus vaccination for recurrent vaginitis. J Hepatol 2008;49:466-73. [https://doi.org/10.1016/j.jhep.2008.05.022] [PMID: 1864655]
10. Muroy T, Kasturi KN, Kafina MJ, Cram DS, Harrison LC, Sasaki T, et al. Antitopoisomerase I monoclonal autoantibodies from sclerodermia patients and tight skin mouse interact with similar epitopes. J Exp Med 1992;175:1103-9. [https://doi.org/10.1084/jem.175.4.1103] [PMID: 13726244] [PMCID: PMC2119171]
11. Kasturi KN, Hatakeyama A, Spiera H, Bona CA. Antifibrillarin autoantibodies present in systemic sclerosis and other connective tissue diseases interact with similar epitopes. J Exp Med 1995;181:1027-36. [https://doi.org/10.1084/jem.181.3.1027] [PMID: 7532674] [PMCID: PMC2191904]
12. Lunardi C, Bason C, Navone R, Mino E, Diamonte G, Corrocher R, et al. Systemic sclerosis immunoglobulin G autoantibodies bind the human cytomegalovirus late protein UL94 and induce apoptosis in human endothelial cells. Nat Med 2000;6:1183-6. [https://doi.org/10.1038/80533] [PMID: 11017152]
13. Mahler M, Mierau R, Gentl E, Bluthner M. Development of a CENP-A/CENP-B-specific immune response in a patient with systemic sclerosis. Arthritis Rheum 2002;46:1866-72. [https://doi.org/10.1002/art.10330] [PMID: 12124871]
14. Lunardi C, Dolcino M, Peterlana D, Bason C, Navone R, Tammassa N, et al. Antibodies against human cytomegalovirus in the pathogenesis of systemic sclerosis: a gene array approach. PLoS Med 2006;3(10)e208. [https://doi.org/10.1371/journal.pmed.0030002] [PMID: 16318412] [PMCID: PMC2198939]
15. Pastano R, Dell’Agnola C, Bason C, Gigli F, Barbiere G, Puccetti A, et al. Antibodies against human cytomegalovirus late protein UL94 in the pathogenesis of scleroderma-like skin lesions in chronic graft-versus-host disease. Int Immunol 2012;24:583-91. [https://doi.org/10.1093/intimm/dxs061] [PMID: 22773152]
16. Dolcino M, Puccetti A, Barbiere G, Bason C, Tiziani E, Ottura A, et al. Infections and autoimmunity: role of human cytomegalovirus in autoimmune endothelial cell damage. Lupus 2015;24:419-32. [https://doi.org/10.1177/0961203314558677] [PMID: 25801885]
17. Bogdanos DP, Sakkas LI. From microbiome to infectome in autoimmunity. Curr Opin Rheumatol 2017;29:369-73. [https://doi.org/10.1093/bo/rwx044] [PMID: 28934824]
18. Dreyfus DH, Farina A, Farina GA. Molecular mimicry, genetic homology, and gene sharing proteomic "molecular fingerprints" using an EBV (Epstein-Barr virus)-derived microarray as a poten-
tial diagnostic method in autoimmune disease. Immunol Res 2018;66:686-95. [https://doi.org/10.1007/s12026-018-9045-0] [PMID: 30552620]

19. Gourh P, Safran SA, Alexander T, Boydens E, Morgan ND, Shah AA, et al. HLA and autoantibodies define scleroderma subtypes and risk in African and European Americans and suggest a role for molecular mimicry. Proc Natl Acad Sci U S A 2020;117:552-62. [https://doi.org/10.1073/pnas.1905901116] [PMID: 31871193] [PMCID: PMC6965366]

20. Bogdanos DP, Baum H, Grasso A, Okamoto M, Butler P, Ma Y, et al. Microbial mimics are major targets of crossreactivity with human pyruvate dehydrogenase in primary biliary cirrhosis. J Hepatol 2004;40:31-9. [https://doi.org/10.1016/s0168-8278(03)00501-4] [PMID: 14872611]

21. Bogdanos DP, Pares A, Baum H, Caballera L, Rigopoulou EI, Ma Y, et al. Disease-specific cross-reactivity between mimicking peptides of heat shock protein of Mycobacterium gordonae and dominant epitope of E2 subunit of pyruvate dehydrogenase is common in Spanish but not British patients with primary biliary cirrhosis. J Autoimmun 2004;22:353-62. [https://doi.org/10.1016/j.jaut.2004.03.002] [PMID: 15120760]

22. Bogdanos DP, Lenzi M, Okamoto M, Rigopoulou EI, Muratori P, Ma Y, et al. Multiple viral/self immunological cross-reactivity in liver kidney microsomal antibody positive hepatitis C virus infected patients is associated with the possession of HLA B51. Int J Immunopathol Pharmacol 2004;17:83-92. [https://doi.org/10.1177/039463200401700112] [PMID: 15000871]

23. Polymeros D, Bogdanos DP, Day R, Atrioli D, Vergani D, Forbes A. Does cross-reactivity between mycobacterium avium paratuberculosis and human intestinal antigens characterize Crohn's disease? Gastroenterology 2006;131:85-96. [https://doi.org/10.1053/j.gastro.2006.04.021] [PMID: 16831593]

24. Koutsoumpas A, Polymeros D, Tsiamoulos Z, Smyk D, Karamanolis G, Triantafyllou K, et al. Peculiar antibody reactivity to human connexin 37 and its microbial mimics in patients with Crohn’s disease. J Crohns Colitis 2011;5:101-09. [https://doi.org/10.1016/j.jcmetry.2011.07.009]

25. Polymeros D, Tsiamoulos ZP, Koutsoumpas AL, Smyk DS, Mytilinaiou MG, Triantafyllou K, et al. Bioinformatic and immunological analysis reveals lack of support for measles virus related mimicry in Crohn’s disease. BMC Med 2014;12,217-24. [https://doi.org/10.1186/s12916-014-0139-9] [PMID: 25168804] [PMCID: PMC4171545]

26. Kanduc D. Potential cross-reactivity between HPV16 L1 protein and sudden death-associated antigens. J Exp Ther Oncol 2011;9:159-65. [PMID: 21699023]

27. Trost B, Kusalik A, Lucchese G, Kanduc D. Bacterial peptides are intensively present throughout the human proteome. Self Nonself 2010;1:71-4. [https://doi.org/10.4161/self.1.1.9589] [PMID: 21559180] [PMCID: PMC3062388]

28. Trost B, Kusalik A, Lucchese G, Kanduc D. Bacterial peptides are intensively present throughout the human proteome. Self Nonself 2010;1:328-34. [https://doi.org/10.4161/self.1.4.13315] [PMID: 21487508] [PMCID: PMC3062388]

29. Garg A, Kumari B, Kumar R, Kumar M. miPepBase: A Database of Experimentally Verified Peptides Involved in Molecular Mimicry. Front Microbiol 2017;8:2053. [https://doi.org/10.3389/fmicb.2017.02053] [PMID: 29109711] [PMCID: PMC5660332]

30. Rath HC, Harfath HH, Ikaeda JS, Grenther WB, Hamm TE Jr., Balish E, et al. Normal luminal bacteria, especially Bacteroides species, mediate chronic colitis, gastritis, and arthritis in HLA-B27 human beta2 microglobulin transgenic rats. J Clin Invest 1996;98:945-53. [https://doi.org/10.1172/JCI118878] [PMID: 8770866] [PMCID: PMC507590]

31. Koutsoumpas A, Mytilinaiou M, Polymeros D, Dalekos G, Bogdanos DP. Anti-Helicobacter pylori antibody responses specific for VacA do not trigger primary biliary cirrhosis-specific antimitochondrial antibodies. Eur J Gastroenterol Hepatol 2009;21:1220. [https://doi.org/10.1097/MEG.0b013e32831e4807]
### Suppl. Table 1A. Topoisomerase I “RQRAVALYFIDKLAL,” BLASTp matches from viruses.

| Description                                      | Score  | E value     | Identities | Positives | Gaps  |
|--------------------------------------------------|--------|-------------|------------|-----------|-------|
| DNA topoisomerase IB [Hokovirus HKV1]            | 45.2   | 4.00E-06    | 14/15(93%) | 14/15(93%)| 0/15(0%) |
| DNA topoisomerase 1b [Megavirus vitis]           | 36.7   | 0.004       | 12/15(80%) | 12/15(80%)| 0/15(0%) |
| DNA topoisomerase 1b [Mimivirus sp. SH]          | 36.7   | 0.004       | 12/15(80%) | 12/15(80%)| 0/15(0%) |
| DNA topoisomerase 1b [Megavirus chilensis]       | 36.7   | 0.004       | 12/15(80%) | 12/15(80%)| 0/15(0%) |
| hypothetical protein [Fowai lake megavirus]      | 36.7   | 0.004       | 12/15(80%) | 12/15(80%)| 0/15(0%) |
| DNA topoisomerase IB [Kosovirus KNV1]            | 36.7   | 0.004       | 12/15(80%) | 12/15(80%)| 0/15(0%) |
| DNA topoisomerase IB [Catovirus CTV1]            | 35.0   | 0.016       | 12/15(80%) | 12/15(80%)| 0/15(0%) |
| DNA topoisomerase IB [Dasosvirus sp.]            | 34.6   | 0.022       | 12/15(80%) | 12/15(80%)| 0/15(0%) |
| DNA topoisomerase 1b [Edafosvirus sp.]           | 34.1   | 0.032       | 11/14(79%) | 11/14(79%)| 0/14(0%) |
| dna topoisomerase 1b [Tupanvirus soda lake]      | 33.3   | 0.063       | 11/15(73%) | 11/15(73%)| 0/15(0%) |
| topoisomerase 1b [Moumouvirus goulette]          | 33.3   | 0.063       | 11/15(73%) | 11/15(73%)| 0/15(0%) |
| topoisomerase 1b [Bodo saltans virus]            | 33.3   | 0.063       | 10/11(91%) | 10/11(90%)| 0/11(0%) |
| topoisomerase 1b [Tupanvirus deep ocean]         | 33.3   | 0.063       | 11/15(73%) | 11/15(73%)| 0/15(0%) |
| topoisomerase 1b [Moumouvirus australiensis]    | 33.3   | 0.063       | 11/15(73%) | 11/15(73%)| 0/15(0%) |
| topoisomerase 1 [Moumouvirus malensis]           | 33.3   | 0.063       | 11/15(73%) | 11/15(73%)| 0/15(0%) |
| DNA topoisomerase 1b [Acanthamoeba polyphaga moumouvirus] | 33.3   | 0.063       | 11/15(73%) | 11/15(73%)| 0/15(0%) |
| DNA topoisomerase 1b [Saud moumouvirus]          | 33.3   | 0.063       | 11/15(73%) | 11/15(73%)| 0/15(0%) |
| Topoisomerase 1b [Faunusvirus sp.]               | 30.3   | 0.72        | 9/10(90%)  | 9/10(90%) | 0/10(0%) |
| putative HNH homing endonuclease [uncultured Caudovirales phage] | 27.8   | 5.8         | 8/10(80%)  | 9/10(90%) | 0/10(0%) |
| virion structural protein [Pseudomonas phage 201phi2-1] | 26.5   | 17          | 7/7(100%)  | 7/7(100%) | 0/7(0%) |
| putative 26S proteasome non-ATPase regulatory subunit 8-like protein | 24.8   | 67          | 7/8(88%)   | 7/8(87%)  | 0/8(0%) |
| Serine/threonine protein kinase [Pandoravirus quercus] | 24.4   | 95          | 7/7(100%)  | 7/7(100%) | 0/7(0%) |
| ribonucleotide reductase of class III (anaerobic), large subunit [Proteus phage PHM2] | 24.4   | 95          | 7/8(88%)   | 7/8(87%)  | 0/8(0%) |
| anaerobic NTP reductase large subunit [Shigella phage vB_SdyM_006] | 24.4   | 95          | 7/8(88%)   | 7/8(87%)  | 0/8(0%) |
| anaerobic NTP reductase large subunit [Proteus phage phiP4-3] | 24.4   | 95          | 7/8(88%)   | 7/8(87%)  | 0/8(0%) |
| large tegument protein [Bovine gammaherpesvirus 6] | 24.4   | 96          | 8/10(80%)  | 8/10(80%) | 0/10(0%) |
| pol protein, partial [Human immunodeficiency virus 1] | 24.0   | 133         | 7/9(78%)   | 7/9(77%)  | 0/9(0%) |
| Putative peptidase [Prokaryotic dsDNA virus sp.] | 24.0   | 135         | 6/6(100%)  | 6/6(100%) | 0/6(0%) |
| modification methylase [Prochlorococcus phage MED4-213] | 24.0   | 135         | 7/10(70%)  | 8/10(80%) | 0/10(0%) |
| RING finger domain protein [Faunusvirus sp.] | 24.0   | 135         | 6/7(86%)   | 7/7(100%) | 0/7(0%) |
| leucyl-tRNA synthetase [Hokovirus HKV1] | 24.0   | 135         | 6/6(100%)  | 6/6(100%) | 0/6(0%) |
| polypeptide [Porcine epidemic diarrhoea virus] | 24.0   | 136         | 6/8(75%)   | 7/8(87%)  | 0/8(0%) |
| polypeptide, partial [Hepatitis C virus subtype 1b] | 23.5   | 190         | 6/8(75%)   | 8/8(100%) | 0/8(0%) |
| minor tail protein [Microbacterium phage Zeta1847] | 23.5   | 191         | 6/8(75%)   | 6/8(100%) | 0/8(0%) |

**MOLECULAR MIMICRY IN SYSTEMIC SCLEROSIS**
**Suppl. Table 1B.** Topoisomerase I “RQRAVALYFIDKLAL,” BLASTp matches from bacteria.

| Description                                                                 | Score | E value | Identities | Positives | Gaps |
|-----------------------------------------------------------------------------|-------|---------|------------|-----------|------|
| hypothetical protein [Ruminococcaceae bacterium]                           | 36.7  | 0.26    | 12/15(80%) | 12/15(80%)| 0/15(0%) |
| asparagine synthase (glutamine-hydrolyzing) [Eggerthellaceae bacterium]    | 35.0  | 1.0     | 10/11(91%) | 11/11(100%) | 0/11(0%) |
| hypothetical protein A2622_08350 [Bdellovibrionales bacterium]              | 32.9  | 5.8     | 9/11(82%)  | 10/11(90%) | 0/11(0%) |
| amino acid permease [Lactobacillus avarius]                                | 32.5  | 8.2     | 9/9(100%)  | 9/9(100%)  | 0/9(0%)  |
| FMN-binding glutamate synthase family protein [CM182 bacterium]            | 32.0  | 12      | 9/10(90%)  | 9/10(90%)  | 0/10(0%) |
| FMN-binding glutamate synthase family protein [Gammaproteobacteria bacterium TMED134] | 32.0  | 12      | 9/10(90%)  | 9/10(90%)  | 0/10(0%) |
| efflux RND transporter permease subunit [Halothiobacillus neapolitanus]    | 30.8  | 33      | 10/15(67%) | 11/15(73%) | 0/15(0%) |
| MFS transporter [Halothiobacillus sp. 15-55-196]                           | 30.8  | 33      | 10/15(67%) | 11/15(73%) | 0/15(0%) |
| asparagine synthase (glutamine-hydrolyzing) [Bacteroides caecimuris]      | 30.8  | 33      | 9/11(82%)  | 10/11(90%) | 0/11(0%) |
| FMN-binding glutamate synthase family protein [Gammaproteobacteria bacterium] | 30.3  | 46      | 8/9(89%)   | 9/9(100%)  | 0/9(0%)  |
| efflux RND transporter permease subunit [Halothiobacillus sp. LS2]         | 29.9  | 66      | 8/10(80%)  | 9/10(90%)  | 0/10(0%) |
| asparagine synthase (glutamine-hydrolyzing) [Eubacterium ventriosum]     | 29.9  | 66      | 8/10(80%)  | 9/10(90%)  | 0/10(0%) |
| tyrosine reombinase [Polymobacter sp. DJ1R-1]                              | 29.9  | 66      | 10/13(77%) | 11/13(84%) | 1/13(7%) |
| cytidylate kinase [Cytophaga aurantiaca]                                    | 29.9  | 66      | 8/9(89%)   | 9/9(100%)  | 0/9(0%)  |
| HNH endonuclease [Salinisphaera japonica]                                  | 29.9  | 66      | 9/13(69%)  | 9/13(69%)  | 0/13(0%) |
| efflux RND transporter permease subunit [Rhzobiales bacterium]             | 29.5  | 93      | 8/10(80%)  | 10/10(100%) | 0/10(0%) |
| lantibiotic dehydratase [Pedobacter yulinensis]                            | 29.5  | 93      | 8/10(80%)  | 8/10(80%)  | 0/10(0%) |
| efllux RND transporter permease subunit [Thiohalosira halophila]          | 29.5  | 93      | 8/9(89%)   | 8/9(89%)   | 0/9(0%)  |
| mechanosensitive ion channel [Mitsuaria sp. 7]                              | 29.5  | 93      | 8/10(80%)  | 9/10(90%)  | 0/10(0%) |
| phosphoenolpyruvate synthase [Niabella ginsenosidivorans]                 | 29.5  | 93      | 8/8(100%)  | 8/8(100%)  | 0/8(0%)  |
| accessory Sec system translocase SecA2 [Paenibacillus sp. Leaf72]         | 29.5  | 93      | 10/12(83%) | 10/12(83%) | 1/12(8%) |
| ABC transporter permease [Desulfovibrio sp.]                               | 29.5  | 93      | 8/8(100%)  | 8/8(100%)  | 0/8(0%)  |
| RagB/SusD family nutrient uptake outer membrane protein [Pedobacter ginsengisoli] | 29.5  | 93      | 8/8(100%)  | 8/8(100%)  | 0/8(0%)  |
| acy-CoA ligase [Proteobacterium rubrum]                                    | 29.5  | 93      | 8/8(100%)  | 8/8(100%)  | 0/8(0%)  |
| RelA/SpoT domain-containing protein [Clostridiales bacterium SYSU GA17129] | 29.5  | 93      | 8/8(100%)  | 8/8(100%)  | 0/8(0%)  |
| DUF3696 domain-containing protein [Vulcanococcus limneticus]              | 29.5  | 93      | 8/9(89%)   | 9/9(100%)  | 0/9(0%)  |
| ABC transporter permease [Candidatus Syntrophosphaera thermopropivorans]  | 29.5  | 93      | 8/8(100%)  | 8/8(100%)  | 0/8(0%)  |
| (d)CMP kinase [Fabibacter pacificus]                                       | 29.5  | 93      | 8/9(89%)   | 8/9(88%)   | 0/9(0%)  |
| SufE family protein [Bacteroides salanitronis]                             | 29.1  | 132     | 8/9(89%)   | 8/9(88%)   | 0/9(0%)  |
MOLECULAR MIMICRY IN SYSTEMIC SCLEROSIS

Suppl. Table 1C. Topoisomerase I “RQRAVALYFIDKLAL,” BLASTp matches from Gram+ bacteria in particular.

| Description                                                                 | Score  | E value | Identities | Positives | Gaps  |
|----------------------------------------------------------------------------|--------|---------|------------|-----------|-------|
| helix-turn-helix domain-containing protein [Bifidobacterium adolescentis]  | 29.1   | 132     | 8/9(99%)   | 8/9(99%)  | 0/9(0%)|
| (d)CMP kinase [Cytophagales bacterium B6]                                  | 29.1   | 132     | 8/8(100%)  | 8/8(100%) | 0/8(0%)|
| cytidylate kinase [ Candidatus Marinimicrobia bacterium]                   | 29.1   | 132     | 8/8(100%)  | 8/8(100%) | 0/8(0%)|
| Predicted hydrolase (HAD superfamily) [Pseudomonas aeruginosa]            | 25.2   | 28      | 8/11(73%)  | 9/11(81%) | 2/11(18%)|
| methyltransferase domain-containing protein [Pseudomonas aeruginosa]       | 25.2   | 28      | 8/11(73%)  | 9/11(81%) | 2/11(18%)|
| hypothetical protein ACS95_27390 [Pseudomonas aeruginosa]                  | 24.4   | 56      | 7/7(100%)  | 7/7(100%) | 0/7(0%)|
| TetR/AcrR family transcriptional regulator [Pseudomonas aeruginosa]       | 24.0   | 79      | 7/8(88%)   | 7/8(88%)  | 0/8(0%)|

Suppl. Table 1D. Topoisomerase I “RQRAVALYFIDKLAL,” BLASTp matches from Enterococci in particular.

| Description                                                                 | Score  | E value | Identities | Positives | Gaps  |
|----------------------------------------------------------------------------|--------|---------|------------|-----------|-------|
| hypothetical protein [Enterococcus raffinosus]                             | 26.5   | 5.7     | 7/7(100%)  | 7/7(100%) | 0/7(0%)|
| GNAT family N-acetyltransferase [Enterococcus mediterraneensis]            | 25.2   | 16      | 7/7(100%)  | 7/7(100%) | 0/7(0%)|
| bifunctional glutamate–cysteine ligase GshA/glutathione synthetase GshB [Enterococcus saccharolyticus] | 25.2   | 16      | 7/7(100%)  | 7/7(100%) | 0/7(0%)|
| AAA family ATPase [Enterococcus avium]                                     | 24.4   | 33      | 6/7(86%)   | 7/7(100%) | 0/7(0%)|
Suppl. Table 1E. Topoisomerase I “RQRAVALYFIDKLAL,” BLASTp matches from *Streptococci* in particular.

| Description                                              | Score | E value | Identities | Positives | Gaps |
|----------------------------------------------------------|-------|---------|------------|-----------|------|
| N-acetylneuraminate lyase [*Streptococcus pneumoniae*]   | 27.8  | 6.5     | 9/12(75%)  | 9/12(75%) | 0/12(0%) |
| hypothetical protein [*Streptococcus pneumoniae*]       | 27.4  | 9.1     | 9/13(69%)  | 9/13(69%) | 2/13(15%) |
| GNAT family N-acetyltransferase [*Streptococcus suis*]   | 27.4  | 9.2     | 9/12(75%)  | 10/12(83%) | 2/12(16%) |
| hypothetical protein SAMN04487837_0195 [*Streptococcus equinus*] | 26.5  | 18      | 7/7(100%)  | 7/7(100%) | 0/7(0%) |
| aminoacyl-tRNA deacylase [*Streptococcus mitis*]         | 25.2  | 53      | 7/7(100%)  | 7/7(100%) | 0/7(0%) |
| MULTISPECIES: IS3 family transposase [*Actinobacteria*]  | 24.8  | 74      | 7/8(88%)   | 7/8(87%)  | 0/8(0%) |

Suppl. Table 1F. Topoisomerase I “RQRAVALYFIDKLAL,” BLASTp matches from *Helicobacter* in particular.

| Description                                                                 | Score | E value | Identities | Positives | Gaps |
|-----------------------------------------------------------------------------|-------|---------|------------|-----------|------|
| ABC-F family ATP-binding cassette domain-containing protein [*Helicobacter canis*] | 26.5  | 9.3     | 7/7(100%)  | 7/7(100%) | 0/7(0%) |
| LptF/LptG family permease [*Helicobacter japonicus*]                        | 25.7  | 19      | 7/7(100%)  | 7/7(100%) | 0/7(0%) |
| tRNA (guanosine(46)-N7)-methyltransferase TrmB [*Helicobacter pylori*]     | 24.8  | 38      | 9/12(75%)  | 9/12(75%) | 2/12(16%) |
### Suppl. Table 2A. CENPA sequence “LQEAAEFLVHLFED” BLASTp matches from bacteria.

| Description | Score | E value | Identities | Positives | Gaps |
|-------------|-------|---------|------------|-----------|------|
| hypothetical protein, partial [Macrococcus caseolyticus] | 41.8 | 0.004 | 13/15(87%) | 14/15(93%) | 0/15(0%) |
| hypothetical protein D8861_11520 [Macrococcus caseolyticus] | 41.8 | 0.004 | 13/15(87%) | 14/15(93%) | 0/15(0%) |
| hypothetical protein, partial [Brucella melitensis] | 41.8 | 0.004 | 13/15(87%) | 14/15(93%) | 0/15(0%) |
| hypothetical protein, partial [Homoserinimonas sp. QAct 916] | 40.5 | 0.011 | 13/15(87%) | 14/15(93%) | 0/15(0%) |
| histone H3, partial [Pseudoocceanicola lipolyticus] | 40.5 | 0.011 | 13/15(87%) | 14/15(93%) | 0/15(0%) |
| hypothetical protein CVM52_26375 [Pseudoocceanicola lipolyticus] | 40.5 | 0.011 | 13/15(87%) | 14/15(93%) | 0/15(0%) |
| hypothetical protein DKP78_14540, partial [Enterococcus faecium] | 40.5 | 0.011 | 13/15(87%) | 14/15(93%) | 0/15(0%) |
| hypothetical protein, partial [Klebsiella pneumoniae] | 40.5 | 0.011 | 13/15(87%) | 14/15(93%) | 0/15(0%) |
| histone H3, partial [Enterococcus faecium] | 40.5 | 0.011 | 13/15(87%) | 14/15(93%) | 0/15(0%) |
| hypothetical protein, partial [Bacillus subtilis] | 40.5 | 0.011 | 13/15(87%) | 14/15(93%) | 0/15(0%) |
| histone H3, partial [Pseudomonas azotofigens] | 38.8 | 0.046 | 12/15(80%) | 13/15(86%) | 0/15(0%) |
| histone H3 [Actinobacteria bacterium] | 38.0 | 0.090 | 12/15(80%) | 13/15(86%) | 0/15(0%) |
| hypothetical protein [Actinobacteria bacterium] | 38.0 | 0.090 | 12/15(80%) | 13/15(86%) | 0/15(0%) |
| hypothetical protein [Neurospora crassa] | 38.0 | 0.091 | 12/15(80%) | 13/15(86%) | 0/15(0%) |
| hypothetical protein, partial [Nitrospina sp. AAD27694] | 38.0 | 0.091 | 12/15(80%) | 13/15(86%) | 0/15(0%) |
| histone H3 [Acinetobacter baumannii] | 38.0 | 0.091 | 12/15(80%) | 13/15(86%) | 0/15(0%) |
| histone H3, partial [Salmonella enterica] | 38.0 | 0.091 | 12/15(80%) | 13/15(86%) | 0/15(0%) |
| histone H3, partial [Vibrio parahaemolyticus] | 38.0 | 0.091 | 12/15(80%) | 13/15(86%) | 0/15(0%) |
| histone H3, partial [Pseudomonas aeruginosa] | 38.0 | 0.091 | 12/15(80%) | 13/15(86%) | 0/15(0%) |

MOLECULAR MIMICRY IN SYSTEMIC SCLEROSIS
| Description                                      | Score | E value | Identities | Positives | Gaps      |
|--------------------------------------------------|-------|---------|------------|-----------|-----------|
| histone H3, partial [Pseudomonas aeruginosa]     | 38.0  | 0.092   | 12/15(80%) | 13/15(86%)| 0/15(0%) |
| hypothetical protein, partial [Klebsiella pneumoniae] | 38.0  | 0.092   | 12/15(80%) | 13/15(86%)| 0/15(0%) |
| hypothetical protein, partial [Acinetobacter baumannii] | 38.0  | 0.092   | 12/15(80%) | 13/15(86%)| 0/15(0%) |
| hypothetical protein, partial [Pseudomonas aeruginosa] | 38.0  | 0.092   | 12/15(80%) | 13/15(86%)| 0/15(0%) |
| hypothetical protein, partial [Acinetobacter baumannii] | 38.0  | 0.092   | 12/15(80%) | 13/15(86%)| 0/15(0%) |
| hypothetical protein, partial [Acinetobacter baumannii] | 38.0  | 0.093   | 12/15(80%) | 13/15(86%)| 0/15(0%) |
| hypothetical protein, partial [Nitriliruptoraceae bacterium ZYF778] | 38.0  | 0.093   | 12/15(80%) | 13/15(86%)| 0/15(0%) |
| hypothetical protein, partial [Acinetobacter baumannii] | 38.0  | 0.093   | 12/15(80%) | 13/15(86%)| 0/15(0%) |
| hypothetical protein, partial [Soehngenia saccharolytica] | 38.0  | 0.093   | 12/15(80%) | 13/15(86%)| 0/15(0%) |
| hypothetical protein, partial [Enterococcus faecium] | 38.0  | 0.093   | 12/15(80%) | 13/15(86%)| 0/15(0%) |
| hypothetical protein, partial [Enterobacter cloacae complex sp. 2DZ2F20B] | 38.0  | 0.093   | 12/15(80%) | 13/15(86%)| 0/15(0%) |
| hypothetical protein, partial [Acinetobacter baumannii] | 38.0  | 0.093   | 12/15(80%) | 13/15(86%)| 0/15(0%) |
| hypothetical protein, partial [Enterobacter cloacae complex sp. 2DZ2F20B] | 38.0  | 0.093   | 12/15(80%) | 13/15(86%)| 0/15(0%) |
| hypothetical protein, partial [Acinetobacter baumannii] | 38.0  | 0.093   | 12/15(80%) | 13/15(86%)| 0/15(0%) |
| hypothetical protein, partial [Fusobacterium nucleatum] | 34.6  | 1.4     | 10/13(77%) | 11/13(84%)| 0/15(0%) |
| hypothetical protein [Curvibacter sp. AE1-3]     | 31.2  | 23      | 9/10(90%)  | 10/10(100%)| 0/10(0%) |
| hypothetical protein [Nitrosomonas sp. Nm134]     | 31.2  | 23      | 9/10(90%)  | 10/10(100%)| 0/10(0%) |
### Table 2B. CENPA sequence “LQEAAEAFVHLFED” BLASTp matches from viruses.

| Description | Score | E value | Identities | Positives | Gaps |
|-------------|-------|---------|------------|-----------|------|
| hypothetical protein DSLPV1_013 [Dishui lake phycodnavirus 1] | 37.5 | 0.002 | 12/15(80%) | 13/15(86%) | 0/15(0%) |
| histone H3 [Sylvanvirus sp.] | 30.8 | 0.51 | 10/15(67%) | 11/15(73%) | 0/15(0%) |
| putative DNA polymerase [Agrobacterium phage 7-7-1] | 27.8 | 5.8 | 8/8(100%) | 8/8(100%) | 0/8(0%) |
| hypothetical protein [Yersinia phage IPS-59] | 26.5 | 16 | 8/9(89%) | 8/9(89%) | 0/9(0%) |
| HNS binding protein [Yersinia phage IPS-69] | 26.5 | 16 | 8/9(89%) | 8/9(89%) | 0/9(0%) |
| hypothetical protein pmac_cds_685 [Pandoravirus macleodensis] | 26.1 | 24 | 7/8(88%) | 7/8(87%) | 0/8(0%) |
| envelope glycoprotein gp120, partial [Human immunodeficiency virus 1] | 25.7 | 33 | 9/14(64%) | 9/14(66%) | 5/14(35%) |
| hypothetical protein [Roseovarius Plymouth podovirus 1] | 25.7 | 33 | 8/11(73%) | 10/11(90%) | 0/11(0%) |
| hypothetical protein [Roseovarius sp. 217 phage 1] | 25.7 | 33 | 8/11(73%) | 10/11(90%) | 0/11(0%) |
| virion protein US2 [Meleagrid alphaherpesvirus 1] | 25.7 | 33 | 7/10(70%) | 8/10(80%) | 0/10(0%) |
| hypothetical protein [Erwinia phage phiEah2] | 24.8 | 66 | 7/9(88%) | 7/9(87%) | 0/9(0%) |
| hypothetical protein ASESINO_96 [Erwinia phage vB_EamM_Asesino] | 24.8 | 66 | 7/9(88%) | 7/9(87%) | 0/9(0%) |
| RNA-dependent RNA polymerase, partial [Turkey picobirnavirus] | 24.8 | 67 | 9/15(60%) | 10/15(66%) | 0/15(0%) |
| RNA-dependent RNA polymerase, partial [Turkey picobirnavirus] | 24.8 | 67 | 9/15(60%) | 10/15(66%) | 0/15(0%) |
| Putative DNA primase [Prokaryotic dsDNA virus sp.] | 24.8 | 67 | 9/15(60%) | 9/15(60%) | 6/15(40%) |
| encapsidation protein 52K [Bat mastadenovirus] | 24.8 | 67 | 7/7(100%) | 7/7(100%) | 0/7(0%) |
| putative DNA polymerase [Prokaryotic dsDNA virus sp.] | 24.8 | 67 | 7/8(88%) | 8/8(100%) | 0/8(0%) |
| hypothetical protein HUXLEY_63 [Erwinia phage vB_EamM_Huxley] | 24.4 | 94 | 7/8(88%) | 7/8(87%) | 0/8(0%) |
| hypothetical protein Tpi103DOM542121_60 [Prokaryotic dsDNA virus sp.] | 24.4 | 95 | 7/8(88%) | 7/8(87%) | 0/8(0%) |
| hypothetical protein GOVbin2277_77 [Prokaryotic dsDNA virus sp.] | 24.0 | 134 | 7/7(100%) | 7/7(100%) | 0/7(0%) |
| HNH endonuclease [Arthrobacter phage Hestia] | 24.0 | 134 | 7/7(100%) | 7/7(100%) | 0/7(0%) |
| hypothetical protein [Yersinia phage fEV-1] | 24.0 | 134 | 7/7(100%) | 7/7(100%) | 0/7(0%) |
| replication associated protein [Cotton leaf curl Multan alphasatellite] | 4.0 | 135 | 6/7(86%) | 7/7(100%) | 0/7(0%) |
| hypothetical protein phLo_113 [Thermus phage phLo] | 24.0 | 135 | 6/7(86%) | 7/7(100%) | 0/7(0%) |
| tapemasure protein [Gordonia phage Tonian] | 24.0 | 136 | 7/7(100%) | 7/7(100%) | 0/7(0%) |
| ape measure protein [Gordonia phage Cucurbita] | 24.0 | 136 | 7/7(100%) | 7/7(100%) | 0/7(0%) |
| tapemasure protein [Gordonia phage CubL] | 24.0 | 136 | 7/7(100%) | 7/7(100%) | 0/7(0%) |
| tape measure protein [Gordonia phage Aphelon] | 24.0 | 136 | 7/7(100%) | 7/7(100%) | 0/7(0%) |
| tape measure protein [Gordonia phage Smoothie] | 24.0 | 136 | 7/7(100%) | 7/7(100%) | 0/7(0%) |
| tape measure protein [Gordonia phage WilliamBoone] | 24.0 | 136 | 7/7(100%) | 7/7(100%) | 0/7(0%) |
| tapemeasure protein [Gordonia phage Bachita] | 24.0 | 136 | 7/7(100%) | 7/7(100%) | 0/7(0%) |
| WSSV530 [Shrimp white spot syndrome virus] | 23.5 | 189 | 7/8(88%) | 7/8(87%) | 0/8(0%) |
| wsv471 [Shrimp white spot syndrome virus] | 23.5 | 189 | 7/8(88%) | 7/8(87%) | 0/8(0%) |
| P13 [Hamiltonella virus APSE1] | 23.5 | 190 | 7/8(88%) | 7/8(87%) | 0/8(0%) |
| lysozyme [Bacteriophage APSE-4] | 23.5 | 190 | 7/8(88%) | 7/8(87%) | 0/8(0%) |
| hypothetical protein SEA_PARADIDDLES_142 [Streptomycoys phage Paradiddles] | 23.5 | 190 | 6/6(100%) | 6/6(100%) | 0/6(0%) |
| hypothetical protein SEA_PEEBS_144 [Streptomycoys phage Ppees] | 23.5 | 190 | 6/6(100%) | 6/6(100%) | 0/6(0%) |
| hypothetical protein 162285194 [Organic Lake phycodnavirus 1] | 23.5 | 190 | 6/6(100%) | 6/6(100%) | 0/6(0%) |
| Description | Score | E value | Identities | Positives | Gaps |
|-------------|-------|---------|------------|-----------|------|
| RNA-dependent RNA polymerase, partial [Porcine picobirnavirus] | 23.5 | 190 | 7/9(78%) | 8/9(88%) | 0/9(0%) |
| hypothetical protein SEA_MILDRED21_153 [Streptomyces phage Mildred21] | 23.5 | 190 | 6/6(100%) | 6/6(100%) | 0/6(0%) |
| peptidase [Streptomyces phage Braelyn] | 23.5 | 190 | 6/6(100%) | 6/6(100%) | 0/6(0%) |
| hypothetical protein SEA_NOOTNOOT_143 [Streptomyces phage NootNoot] | 3.5 | 190 | 6/6(100%) | 6/6(100%) | 0/6(0%) |
| peptidase [Streptomyces phage Teutsch] | 3.5 | 190 | 6/6(100%) | 6/6(100%) | 0/6(0%) |
| hypothetical protein SEA_SUSHI23_147 [Streptomyces phage Sushi23] | 3.5 | 190 | 6/6(100%) | 6/6(100%) | 0/6(0%) |
| peptidase [Streptomyces phage Starbow] | 3.5 | 190 | 6/6(100%) | 6/6(100%) | 0/6(0%) |
| peptidase [Streptomyces phage Daubenski] | 3.5 | 190 | 6/6(100%) | 6/6(100%) | 0/6(0%) |
| peptidase [Streptomyces phage Karimac] | 3.5 | 190 | 6/6(100%) | 6/6(100%) | 0/6(0%) |
| peptidase [Streptomyces phage Tribute] | 3.5 | 190 | 6/6(100%) | 6/6(100%) | 0/6(0%) |
| peptidase [Streptomyces phage EGole] | 3.5 | 190 | 6/6(100%) | 6/6(100%) | 0/6(0%) |
| peptidase [Streptomyces phage Eve] | 3.5 | 190 | 6/6(100%) | 6/6(100%) | 0/6(0%) |
| peptidase [Streptomyces phage Wipeout] | 3.5 | 190 | 6/6(100%) | 6/6(100%) | 0/6(0%) |
| peptidase [Streptomyces phage LukeCage] | 3.5 | 190 | 6/6(100%) | 6/6(100%) | 0/6(0%) |
| hypothetical protein SEA_YABOI_154 [Streptomyces phage Yaboi] | 3.5 | 190 | 6/6(100%) | 6/6(100%) | 0/6(0%) |
| peptidase [Streptomyces phage Wofford] | 3.5 | 190 | 6/6(100%) | 6/6(100%) | 0/6(0%) |
| peptidase [Streptomyces phage StarPlatinum] | 3.5 | 190 | 6/6(100%) | 6/6(100%) | 0/6(0%) |
| hypothetical protein PBI_JAY2JAY_152 [Streptomyces phage Jay2Jay] | 23.5 | 191 | 6/6(100%) | 6/6(100%) | 0/6(0%) |
| hypothetical protein SEA_WARPY_151 [Streptomyces phage Warpy] | 23.5 | 191 | 6/6(100%) | 6/6(100%) | 0/6(0%) |
| repeat element protein-c18.1 [Hyposoter fugitivus ichnovirus] | 23.5 | 191 | 6/6(100%) | 6/6(100%) | 0/6(0%) |
| integrase family protein [uncultured Mediterranean phage] | 23.5 | 192 | 7/10(70%) | 9/10(90%) | 0/10(0%) |
| hypothetical protein YASMINEVIRUS_1387 [Yasminevirus sp. GU-2018] | 23.5 | 192 | 8/9(88%) | 8/9(88%) | 1/9(11%) |
| large T antigen, partial [Tasmanian devil-associated polyoma-like virus 2] | 23.5 | 192 | 8/12(67%) | 10/12(83%) | 1/12(8%) |
| Description                                                                 | Score | E value   | Identities | Positives | Gaps   |
|-----------------------------------------------------------------------------|-------|-----------|------------|-----------|--------|
| histone H3-like centromeric protein H3v [Emmonis sp. CAC-2015a]             | 51.1  | 6.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| hypothetical protein AN6554.2 [Aspergillus nidulans FGSC A4]                | 51.1  | 6.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| hypothetical protein V501_04928 [Pseudogymnosascus sp. VKM F-4519 [FW-2642] | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| hypothetical protein AC578_6719 [Pseudocercospora eumusae]                  | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| hypothetical protein AC579_7423 [Pseudocercospora musae]                    | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| 94d01dbe-7812-426c-b7ef-62d5d5cc3986 [Thermothielavioides generis]         | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| hypothetical protein AUEXF2481DRAFT_64859 [Aureobasidium subglaciale]       | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| centromeric DNA-binding histone H3-like protein cse4 [Pseudogymnosascus destructans] | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| uncharacterized protein THITE_113981 [Thermothielavioides terrestis NRRL 8126] | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone H3 [Kwoniella heveanensis CBS 569]                                  | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone H3 [Kwoniella heveanensis BCC8338]                                 | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| Similar to Histone H3-like centromeric protein crp1; acc. no. Q9Y812 [Pyronema omphalodes CBS 100304] | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone H3-like centromeric protein crp1 [Smittium mucronatum]             | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| centromere protein Cse4, putative [Talaromyces marneffei ATCC 18224]        | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| hypothetical protein BHQ10_008142 [Talaromyces anastotiae]                  | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| Histone-fold [Penicillium sp. 'occatianis']                                | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| centromere protein [Talaromyces cellulolyticus]                            | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| hypothetical protein ZTR_08177 [Talaromyces verruculosus]                   | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| Histone 3-like protein [Rasamsonnia emersonii CBS 393.64]                    | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| centromere protein Cse4, putative [Talaromyces stipitatus ATCC 10500]       | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| hypothetical protein ASPACDRAFT_46181 [Aspergillus aculeatus ATCC 16872]    | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone-fold-containing protein [Aspergillus fijiensis CBS 313.88]           | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| Uncharacterized protein DSM745_04281 [Aspergillus murumensis]               | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| putative centromere protein Cse4 [Aspergillus novofumigatus IBT 16808]     | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone-fold-containing protein [Aspergillus violaceofuscus CBS 115571]     | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone-fold-containing protein [Aspergillus japonicus CBS 114.5]           | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| hypothetical protein Egran_04734 [Elaphomyces granulatus]                   | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| Histone H3-like centromeric protein cse-4 [Talaromyces islandicus]          | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| putative centromere protein Cse4 [Aspergillus bruneoviolaceus CBS 621.78]  | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone H3-like centromeric protein A [Bos indicus x Bos taurus]            | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| putative centromere protein Cse4 [Aspergillus uvarum CBS 121591]           | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| centromeric DNA-binding histone H3-like protein cse4 [Monascus purpureus]   | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| hypothetical protein ASPGLDRAFT_49919 [Aspergillus glaucus CBS 516.65]      | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| TPA: Histone H3-like centromeric protein A-like [Bos taurus]                | 51.1  | 7.00E-07  | 100.00%    | 15/15(100%) | 0/15(0%) |
| Description                                                                 | Score | E value     | Identities | Positives | Gaps |
|----------------------------------------------------------------------------|-------|-------------|------------|-----------|------|
| TPA: hypothetical protein similar to histone H3 (Broad) [Aspergillus nidulans FGSC A4] | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| PREDICTED: histone H3-like centromeric protein A [Bison bison bison]        | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone-fold-containing protein [Aspergillus indologenus CBS 114.80]        | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| putative centromere Cae4 [Aspergillus aculeatinus CBS 121060]               | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone H3 variant [Aspergillus ruber CBS 135680]                          | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| hypothetical protein ASPZODRAFT_135809 [Penicilliopsis zonata CBS 506.65]  | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| hypothetical protein S65_03462 [Aspergillus cristatus]                     | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone H3-like centromeric protein cse-4 [Helicocarpus griseus UAMH5409] | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone H3 [Kwoniella mangrovesiensis CBS 8507]                             | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone H3 variant [Aspergillus vadensis CBS 113365]                       | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone H3 variant [Aspergillus kawachi IFO 4308]                          | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone H3-like centromeric protein cse-4 [Aspergillus bombycis]           | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone H3-like centromeric protein hH3v [Blastomycetes percurus]          | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone H3 variant [Aspergillus eucalypticola CBS 101740]                  | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone H3-like centromeric protein A [Mits pahari]                        | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone H3 variant [Aspergillus neonger CBS 115656]                        | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone H3-like centromeric protein CSE4 [Kwoniella bestiolae CBS 10118]  | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone H3-like centromeric protein H3V [Blastomyces percurus]             | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| putative centromere protein Cae4 [Aspergillus homomorphus CBS 101889]     | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone H3-like centromeric protein CSE4 [Aspergillus ibericus CBS 121593] | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone H3-like centromeric protein cse-4 [Aspergillus nomius NRRL 13137] | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone H3-like centromeric protein cse-4 [Aspergillus pseudocaelatus]     | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone H3-like centromeric protein cse-4 [Aspergillus alliaceus]          | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone H3-like centromeric protein [Aspergillus candidus]                 | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone H3-like centromeric protein [Aspergillus caelatus]                 | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone H3-like centromeric protein [Aspergillus ruber]                    | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| putative centromere protein Cae4 [Aspergillus candidus]                    | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone H3-like centromeric protein cse-4 [Aspergillus ibericus CBS 121593] | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| histone H3 variant [Aspergillus sclerotialis CBS 115572]                   | 51.1  | 7.00E-07    | 100.00%    | 15/15(100%) | 0/15(0%) |
| Description                                                                 | Score | E value    | Identities | Positives | Gaps   |
|-----------------------------------------------------------------------------|-------|------------|------------|-----------|--------|
| histone H3-like centromeric protein cse-4 [Aspergillus scleroticharmonarius | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
| CBS 121057]                                                                 |       |            |            |           |        |
| histone H3 variant [Aspergillus saccharolyticus JOP 1030-1]                 | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
| histone H3 [Histoplasma capsulatum NAm1]                                    | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
| histone H3-like centromeric protein A [Blastomyces gilchristi SLH14081]    | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
| hypothetical protein ASPCADRAFT_177896 [Aspergillus carbonarius ITEM 5010] | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
| histone H3 variant, putative [Aspergillus fischeri NRRL 181]               | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
| centromere protein Cse4, putative [Aspergillus fumigatus AF293]             | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
| histone H3-like centromeric protein H3v [Emmonsia crescens]                | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
| histone H3-like centromeric protein H3v [Aspergillus lentulus]             | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
| centromere protein Cse4 [Aspergillus fumigatus Z5]                         | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
| centromere protein Cse4 [Aspergillus fumigatus var. RP-2014]               | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
| histone-fold-containing protein [Aspergillus leporis]                      | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
| histone H3-like centromeric protein A [Emmonsia crescens UAMH 3008]        | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
| histone H3 [Byssoclamys spectabilis]                                       | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
| histone-fold-containing protein [Aspergillus tamarii]                      | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
| histone H3-like centromeric protein cse-4 [Aspergillus udagawai]           | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
| histone H3 [Aspergillus terreus NIH2624]                                    | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
| centromeric DNA-binding histone H3-like protein cse4 [Aspergillus tanner]  | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
| histone H3-like centromeric protein cnp1 [Blastomyces parvus]              | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
| histone H3-like centromeric protein H3v [Aspergillus thermomutatus]        | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
| hypothetical protein ATETN484_0008013300 [Aspergillus terreus]              | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
| histone H3 [Aspergillus steyni IBT 23098]                                  | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
| histone H3-like centromeric protein H3v [Aspergillus turcosus]             | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
| histone H3 [Aspergillus avenaceus]                                         | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
| histone H3-like centromeric protein CSE4 [Paracoccidioides brasiliensis Pb18] | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
| histone H3 [Paracoccidioides lutzii Pb01]                                  | 51.1  | 7.00E-07   | 100.00%    | 15/15(100%) | 0/15(0%)|
### Suppl. Table 2D. CENPA sequence “LQEAEFLVHLFED” BLASTp matches from Gram+ bacteria, in particular.

| Description                                                                 | Score  | E value       | Identities | Positives | Gaps       |
|----------------------------------------------------------------------------|--------|---------------|------------|-----------|------------|
| hypothetical protein, partial [Macrococcus caseolyticus]                   | 41.8 bits(91) | 6.00E-04      | 13/15(87%) | 14/15(93%) | 0/15(0%)   |
| hypothetical protein D6861_11520 [Macrococcus caseolyticus]                | 41.8 bits(91) | 6.00E-04      | 13/15(87%) | 14/15(93%) | 0/15(0%)   |
| hypothetical protein DKP78_14540, partial [Enterococcus faecium]           | 40.5 bits(88) | 0.002         | 13/15(87%) | 14/15(93%) | 0/15(0%)   |
| histone H3, partial [Soehngenia saccharolytica]                            | 40.5 bits(88) | 0.002         | 13/15(87%) | 14/15(93%) | 0/15(0%)   |
| histone H3 [Paenibacillus sp. IHB B 3415]                                  | 40.5 bits(88) | 0.002         | 13/15(87%) | 14/15(93%) | 0/15(0%)   |
| hypothetical protein QW71_36435 [Paenibacillus sp. IHB B 3415]             | 40.5 bits(88) | 0.002         | 13/15(87%) | 14/15(93%) | 0/15(0%)   |
| histone H3 [Bacillus paralicheniformis]                                    | 38.8 bits(84) | 0.007         | 12/15(80%) | 13/15(86%) | 0/15(0%)   |
| hypothetical protein, partial [Enterococcus faecium]                      | 38.0 bits(82) | 0.015         | 12/15(80%) | 13/15(86%) | 0/15(0%)   |

### Suppl. Table 2E. CENPA sequence “LQEAEFLVHLFED” BLASTp matches from enterococci, in particular.

| Description                                                                 | Score  | E value       | Identities | Positives | Gaps       |
|----------------------------------------------------------------------------|--------|---------------|------------|-----------|------------|
| hypothetical protein DKP78_14540, partial [Enterococcus faecium]           | 40.5 bits(88) | 6.00E-05      | 13/15(87%) | 14/15(93%) | 0/15(0%)   |
| hypothetical protein, partial [Enterococcus faecium]                      | 38.0 bits(82) | 5.00E-04      | 12/15(80%) | 13/15(86%) | 0/15(0%)   |
| ABC transporter permease/substrate-binding protein [Enterococcus sulfurus] | 27.8 bits(58) | 2.0           | 8/8(100%)  | 8/8(100%)  | 0/8(0%)    |
| HAD-IA family hydrolase, partial [Enterococcus faecalis]                  | 26.9 bits(56) | 4.0           | 8/11(73%)  | 8/11(72%)  | 0/11(0%)   |
| MULTISPECIES: HAD family hydrolase [Bacilli]                               | 26.9 bits(56) | 4.0           | 8/11(73%)  | 8/11(72%)  | 0/11(0%)   |
| HAD family hydrolase [Enterococcus faecalis]                              | 26.9 bits(56) | 4.0           | 8/11(73%)  | 8/11(72%)  | 0/11(0%)   |
| HAD family hydrolase [Enterococcus faecalis]                              | 26.9 bits(56) | 4.0           | 8/11(73%)  | 8/11(72%)  | 0/11(0%)   |
| HAD hydrolase, family IA, variant 1 [Enterococcus faecalis TX0411]        | 26.9 bits(56) | 4.0           | 8/11(73%)  | 8/11(72%)  | 0/11(0%)   |
| Phosphoglycolate phosphatase [Enterococcus faecalis GA2]                  | 26.9 bits(56) | 4.0           | 8/11(73%)  | 8/11(72%)  | 0/11(0%)   |
| HAD hydrolase, family IA, variant 1 [Enterococcus faecalis EnGen0297]     | 26.9 bits(56) | 4.0           | 8/11(73%)  | 8/11(72%)  | 0/11(0%)   |
| HAD family hydrolase [Enterococcus faecalis]                              | 26.9 bits(56) | 4.0           | 8/11(73%)  | 8/11(72%)  | 0/11(0%)   |
| phosphopantothenate–cysteine ligase [Enterococcus mundtii]                | 25.7 bits(53) | 11            | 8/10(80%)  | 8/10(80%)  | 0/11(0%)   |
| phosphopantothenate–cysteine ligase [Enterococcus mundtii]                | 25.7 bits(53) | 11            | 8/10(80%)  | 8/10(80%)  | 0/11(0%)   |
| phosphopantothenate–cysteine ligase [Enterococcus mundtii]                | 25.7 bits(53) | 11            | 8/10(80%)  | 8/10(80%)  | 0/11(0%)   |
| hypothetical protein [Enterococcus faecium]                               | 25.7 bits(53) | 11            | 8/10(80%)  | 8/10(80%)  | 0/11(0%)   |
| hypothetical protein A5852_003495 [Enterococcus faecium]                  | 25.7 bits(53) | 11            | 8/10(80%)  | 8/10(80%)  | 0/11(0%)   |
Suppl. Table 2F. CENPA sequence “LQEAAEFLVHLFED” BLASTp matches from streptococci, in particular.

| Description                                                   | Score | E value | Identities | Positives | Gaps   |
|---------------------------------------------------------------|-------|---------|------------|-----------|--------|
| adenine-specific methyltransferase [Streptococcus pneumoniae]| 27.8  | 6.5     | 9/12(75%)  | 9/12(75%) | 3/12(25%) |
| IS256 family transposase [Streptococcus thermophilus]        | 27.8  | 6.5     | 10/14(71%) | 11/14(78%)| 0/14(0%) |
| IS256 family transposase [Streptococcus thermophilus]        | 27.8  | 6.5     | 10/14(71%) | 11/14(78%)| 0/14(0%) |
| IS256 family transposase [Streptococcus thermophilus]        | 27.8  | 6.5     | 10/14(71%) | 11/14(78%)| 0/14(0%) |
| IS1191, transposase, IS256 family [Streptococcus thermophilus LMG 18311] | 27.8  | 6.5     | 10/14(71%) | 11/14(78%)| 0/14(0%) |
| hydrolase [Streptococcus agalactiae]                         | 26.9  | 13      | 8/11(73%)  | 8/11(72%) | 0/11(0%) |
| methyltransferase [Streptococcus massiliensis]               | 26.9  | 13      | 8/9(89%)   | 8/9(88%)  | 0/9(0%)  |
| class I SAM-dependent rRNA methyltransferase [Streptococcus massiliensis] | 26.9  | 13      | 8/9(89%)   | 8/9(88%)  | 0/9(0%)  |
| GNAT family N-acetyltransferase [Streptococcus sp. DD12]     | 26.5  | 19      | 9/12(75%)  | 10/12(83%)| 0/12(0%) |
| hypothetical protein, partial [Streptococcus suis]           | 26.5  | 19      | 7/7(100%)  | 7/7(100%) | 0/7(0%)  |
| hypothetical protein, partial [Streptococcus suis]           | 26.5  | 19      | 7/7(100%)  | 7/7(100%) | 0/7(0%)  |
| hypothetical protein, partial [Streptococcus suis]           | 26.5  | 19      | 7/7(100%)  | 7/7(100%) | 0/7(0%)  |
| hypothetical protein, partial [Streptococcus suis]           | 26.5  | 19      | 7/7(100%)  | 7/7(100%) | 0/7(0%)  |
| hypothetical protein, partial [Streptococcus suis]           | 26.5  | 19      | 7/7(100%)  | 7/7(100%) | 0/7(0%)  |
| zinc metalloprotease ZmpC [Streptococcus suis]               | 26.5  | 19      | 7/7(100%)  | 7/7(100%) | 0/7(0%)  |
| hypothetical protein, partial [Streptococcus suis]           | 26.5  | 19      | 7/7(100%)  | 7/7(100%) | 0/7(0%)  |
| hypothetical protein, partial [Streptococcus suis]           | 26.5  | 19      | 7/7(100%)  | 7/7(100%) | 0/7(0%)  |
| hypothetical protein, partial [Streptococcus suis]           | 26.5  | 19      | 7/7(100%)  | 7/7(100%) | 0/7(0%)  |
| hypothetical protein, partial [Streptococcus suis]           | 26.5  | 19      | 7/7(100%)  | 7/7(100%) | 0/7(0%)  |
| hypothetical protein, partial [Streptococcus suis]           | 26.5  | 19      | 7/7(100%)  | 7/7(100%) | 0/7(0%)  |

Suppl. Table 2G. CENPA sequence “LQEAAEFLVHLFED” BLASTp matches from Helicobacter species, in particular.

| Description                                                   | Score | E value | Identities | Positives | Gaps   |
|---------------------------------------------------------------|-------|---------|------------|-----------|--------|
| nickel-dependent hydrogenase large subunit [Helicobacter aurati] | 29.1  | 1.2     | 11/19(58%) | 11/19(57%)| 7/19(36%) |
| nickel-dependent hydrogenase large subunit [Helicobacter sagini] | 27.8  | 3.3     | 11/19(58%) | 12/19(63%)| 7/19(36%) |
| hypothetical protein [Helicobacter jachii]                    | 26.1  | 13      | 7/8(86%)   | 7/8(87%)  | 0/8(0%)  |
| nickel-dependent hydrogenase large subunit [Helicobacter sp. MIT 14-3879] | 26.1  | 13      | 10/19(53%) | 10/19(52%)| 7/19(36%) |
| 16S rRNA (guanine) methyltransferase RsmD [Helicobacter sp.]   | 25.7  | 19      | 7/9(73%)   | 7/9(73%)  | 0/9(0%)  |
| uracil-DNA glycosylase [Helicobacter pylori]                   | 25.2  | 27      | 8/13(62%)  | 9/13(69%) | 4/13(30%) |
**Suppl. Table 3.** Taxid ID numbers used for BLASTp search analysis.

| Organism                  | Taxid ID Number |
|---------------------------|-----------------|
| Human                     | 9606            |
| Eukaryotes                | 2759            |
| Bacteria                  | 2               |
| Gram positive bacteria    | 1239            |
| Enterococcus              | 1350            |
| Streptococcus             | 1301            |
| Helicobacter              | 209             |
| Brucella                  | 234             |
| Staphylococcus            | 1279            |
| Viruses                   | 10239           |
| Herpesviridae             | 10292           |
| Epstein-Barr virus        | 10376           |
| Human cytomegalovirus     | 10359           |
| Hepatitis C virus         | 11103           |