Available online at www.elixirpublishers.com (Elixir International Journal)

Bio Physics

Elixir Bio Phys. 60 (2013) 16189-16193

ISSN: 2229-712X

Identification of rheumatoid factors in sjogren's syndrome and computational study on domain prediction

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ARTICLE INFO

Article history:

Received: 15 May 2013;

Received in revised form:

17 June 2013;

Accepted: 4 July 2013;

Keywords

Immunoglobulin,

Rheumatoid arthiritis,

Sjsyndrome,

Domain,

Epidermal growth factor.

ABSTRACT

We have observed that the Immunoglobulin domain (IGv) is mainly present in all those sequences. These observations also suggests that the predicted values of IGv domain is predominantly present in all those sequences and slightly IGc1 domain and IG like domain is also present. On the basis of lower E-value IGv domain is highly conserved in the sequence, from position 17 to 98, and IGc1 domain from 147 to 220.Each sequence has consist of varied composition of CCP (Complementary control proteins), EGF (Epidermal Growth Factor), EGFCA, VWA (Von Wille Brand type A domain), IG, IGc2, TSP1, TROVE, Calireticulin family, RING domain, BBOX, PRY, SPRY with different E-value. Finally, We have concluded that on the basis of lower E-value vWFA(97-214), TROVE(18-369), IGc(183-273), SPRY(86-220), La(13-48), MHC Class I An alpha 1, 2 (1-178) these listed domains are highly conserved.

Introduction

Autoimmune diseases are disorders caused by an immune response directed against the body's own organs, tissues and cells. These are the diseases caused by the body producing an inappropriate immune response against its own tissues. Autoimmune diseases are commonly considered complex immune disorders. Despite their clinical diversity, they have one similarity, namely the dysfunction of the immune system. It is suspected that genetic defects play a role in the etiology of these diseases. Although their etiology is unclear these diseases share certain similarities at the molecular level. The etiopathogenesis of many autoimmune disorders has not been identified. Avirulent and commensal bacteria, which may have important role as initiating factors in the pathogenesis of autoimmune disorders such as PBC and AIP, will be emphasized. (Ref 1)

Rheumatoid Arthritis

Biologic therapies have revolutionized the treatment of rheumatic diseases in the past decade. As with any drugs, however, a variety of important safety concerns affect the choice and use of these agents. Several issues, such as the risk of infection, malignancy, or administration reactions, apply to all of these compounds, although some conditions that affect patient selection and management within these categories seem to be specific to particular biologic treatments. Other safety concerns with biologic agents, such as congestive heart failure, demyelinating disease, and hyperlipidemia, are associated with individual agents. (Ref 2)

Rheumatoid factors are antibodies directed against IgG that may confound immunogenicity testing for therapeutic monoclonal antibodies. We developed antigen-binding assays to monitor anti-drug-antibody (ADA) responses against infliximab and adalimumab using Fab2 fragments of the drug. This avoids possible detection of rheumatoid factor activity. During development of these assays, a number of sera from patients before treatment as well as several healthy control sera were tested positive. None of these sera contained antibodies specific for the therapeutic mAb. Instead, they were found to contain anti-hinge antibodies. (Ref 3)

Rheumatoid arthritis (RA) is a systemic autoimmune disease whose main characteristic is persistent joint inflammation that results in joint damage and loss of function. Although RA is more common in females, extra-articular manifestations of the disease are more common in males. The extra-articular manifestations of RA can occur at any age after onset. It is characterized by destructive polyarthritis and extra-articular organ involvement, including the skin, eye, heart, lung, renal, nervous and gastrointestinal systems. The frequency of extra-articular manifestations in RA differs from one country to another. Extra-articular organ involvement in RA is more frequently seen in patients with severe, active disease and is associated with increased mortality. (Ref 4)

Sjogren's Syndrome

Renal involvement in primary Sjogren's syndrome is not uncommon. Autoimmune tubulointerstitial disorders and distal renal tubular acidosis (dRTA) account for majority of the cases of renal involvement. While dRTA may precede the onset of sicca syndrome in pSS, nephrocalcinosis as a presenting manifestation of pSS is rare. Sjogren's syndrome is an autoimmune disease in which the body's immune system mistakenly attacks its own moisture producing glands for unknown reasons. Normally, the immune system works to protect us from disease by destroying harmful invading organisms like viruses and bacteria. (Ref 5)

Domain Prediction

Protein residue-residue contact prediction is important for protein model generation and model evaluation. A conformation

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Table 1: Domain Prediction of Rheumatoid factor (Sjogren's syndrome)

S. No	AC Number(NCBI)	Sequence Name	Domain	Sequence Position	E-Value
1.	4426625	AAD20457.1	IGv	1 to 66	2.96e-15
2.	4426623	AAD20456.1	IGv	1 to 67	2.06e-14
3.	4426621	AAD20455.1	IGv	1 to 67	4.81e-15
4.	4426619	AAD20454.1	IGv	1 to 66	1.92e-14

Table 2: Domain Prediction of Rheumatoid factor (Rheumatoid arthritis)

S. No	AC No. (NCBI)	Sequence Name	Domain	Sequence Position	E-Value
1.	146387536	2J6E	IGv	36 to 110	4.99e-22
2.	146387535		IGc1	152 to 226	1.43e-31
3.	146387534	2J6E	IGv	28 to 110	3.39e-33
4.	146387533		IGc1	152 to 227	3.88e-04
5.	146387532	2J6E	IG-Like domain	41 to 116	2.34e-02
6.	146387531		IGc1	147 to 220	1.21e-38
7.	4261687	AAD13987.1	IGv	3 to 75	2.29e-21
8.	4261686	AAD13986.1	IGv	3 to 75	2.09e-24
9.	452884	AAB28703.1	IGv	3 to 75	4.31e-26
10.	509804	CAA84376.1	IGv	17 to 98	5.06e-32
11.	509802	CAA84375.1	IGv	18 to 90	4.45e-19
12.	509800	CAA84374.1	IGv	17 to 98	1.03e-32
13.	509798	CAA51998.1	IGv	17 to 98	1.26e-32
14.	685026	AAB30941.1	IGv	17 to 89	2.52e-18
15.	685022	AAB30939.1	IGv	17 to 92	3.85e-14
16.	7717458	AAB30944.2	IGv	10 to 91	2.05e-32
17.	685034	AAB30945.1	IGv	10 to 90	1.40e-34
18.	685028	AAB30942.1	IGv	10 to 91	7.55e-31
19.	4379083	CAA75162.1	IGv	10 to 90	3.75e-26
20.	4379082	CAA75161.1	IGv	10 to 90	3.42e-29
21.	4379081	CAA75160.1	IGv	10 to 90	8.88e-28
22.	4379080	CAA75159.1	IGv	10 to 91	2.95e-33
23.	4379079	CAA75158.1	IGv	10 to 91	5.13e-33
24.	4379078	CAA75157.1	IGv	10 to 91	5.50e-33
25.	4379077	CAA75156.1	IGv	10 to 90	3.42e-29
26.	4379076	CAA75155.1	IGv	10 to 92	7.55e-31
27.	4379075	CAA75154.1	IGv	10 to 90	3.75e-26
28.	4379074	CAA75153.1	IGv	10 to 91	1.03e-32
29.	4379073	CAA75152.1	IGv	10 to 91	2.39e-33
30.	4379072	CAA75151.1	IGv	10 to 91	2.39e-33
31.	185688	AAA58814.1	IGv	36 to 117	1.81e-33
32.	12750747	AAA20160.2	IGv	18 to 90	1.97e-20
33.	12750746	AAA20159.2	IGv	14 to 86	1.33e-17
34.	307023	AAA20178.1	IGv	17 to 98	5.55e-29
35.	307021	AAA20177.1	IGv	17 to 98	9.66e-29
36.	307019	AAA20176.1	IGv	17 to 98	5.55e-29
37.	307017	AAA20175.1	IGv	13 to 94	1.23e-30
38.	307015	AAA20174.1	IGv	17 to 97	1.64e-31
39.	307013	AAA20173.1	IGv	17 to 98	1.12e-33
40.	307011	AAA20172.1	IGv	17 to 98	1.64e-31
41.	307009	AAA20171.1	IGv	17 to 98	2.90e-32
42.	307007	AAA20170.1	IGv	17 to 99	2.25e-29
43.	307005	AAA20169.1	IGv	17 to 98	5.72e-31
44.	307001	AAA20168.1	IGv	18 to 91	1.43e-22
45.	306999	AAA20167.1	IGv	18 to 91	5.06e-23
46.	306997	AAA20166.1	IGv	18 to 90	2.33e-22
47.	306995	AAA20165.1	IGv	18 to 90	2.49e-22
48.	306993	AAA20164.1	IGv	14 to 86	6.68e-23
49.	298557	AAB25740.1	IGv	17 to 89	1.66e-18
50.	306991	AAA20163.1	IGv	18 to 91	1.05e-20
51.	306989	AAA20162.1	IGv	18 to 90	2.49e-22
52.	306987	AAA20161.1	IGv	14 to 91	2.59e-20
53.	306981	AAA20158.1	IGv	18 to 90	1.51e-21
54.	3659942	1ADQ	IGv	16 to 88	6.29e-19
			IGc1	130 to 204	4.11e-32
55.	3659940	1ADQ	IG Like	19 to 94	4.52e-02
			IGc1	125 to 198	2.77e-38
56.	477433	A49002	IGv	17 to 99	3.52e-31
57.	913656	AAB33540.1	IGv	17 to 97	9.21e-35
58.	58424195	1906410B	IGv	18 to 89	1.13e-20
59.	107596	|S21916	IGv	36 to 117	1.55e-27
60.	125809	P04207.2	IGv	38 to 110	2.86e-22
61.	125807	P04206.1	IGv	18 to 91	3.47e-21

Table 3; Domain Prediction of SSA/Anti-Ro (Sjogren's syndrome)

S. No	AC No. (NCBI)	Sequence Name	Domain	Sequence Position	E-Value
1. 2.	189491647| 189491645	NP_001121637.1 NP_694946.2	CCP	81 to 134	1.14e-14
			EGF	139 to 172	1.29e-08
			EGF CA	178 to 223	3.87e-12
			EGF CA	224 to 273	6.16e-06
3.	118572606|	NP_114141.2	VWA	39 to 213	3.16e-01
			IG	436 to 517	5.89e-01
			IGc2	624 to 688	1.19e-10
			TSP1	4646 to 4698	2.27e-17
			EGFCA	5315 to 5355	1.08e-10
			EGF	5475 to 5517	1.66e+01
4.	153266841	NP_000033.2	CCP(Complement control protein)	142 to 200	1.10e-07
				205 to 260	1.61e-14
				84 to 137	1.95e-13
5.	108796061	NP_001035829.1	TROVE	1 to 94	2e-25
			vWFA	97 to 214	0.001
6.	108796056	NP_001035828.1	TROVE	18 to 369	1e-119
			vWFA	372 to 489	4e-04
7.	31377800	|NP_004591.2	TROVE	18 to 369	7e-121
			vWFA	372 to 489	5e-04
8.	5102681	CAB45253.1	IGv	18 to 90	1.04e-19
9.	5102679	CAB45252.1	IGv	17 to 98	2.47e-35
10.	5102677	CAB45251.1|	IGv	17 to 92	3.17e-24
11.	5102675	CAB45250.1	IGv	17 to 98	1.87e-35
12.	4757900|	NP_004334.1	Calreticulin family	22 to 332	6e-121
13.	18088117	AAH20493.1	Calreticulin family	22 to 332	6e-121
14. 23.	4757900 4757900	NP_004334.1 |NP_004334.1	Calreticulin family	22 to 332	6e-121
15.	15982946	AAL11501.1	RING domain	16 to 60	5.30e-09
			BBOX	93 to 134	5.30e-09
			PRY	302 to 354	7.37e-26
			SPRY	355 to 482	2.00e-28
16.	|1561517	BAA08500.1	IGc1	222 to 293	5.51e-24
17.	3522976	BAA32612.1	IGc1	222 to 293	3.75e-26
18. 19. 21. 22. 24.	747927 337485 133250 15208660 14790039	AAA79867.1 AAA36581.1 P19474.1 NP_003132.2 AAH10861.1	RING domain	16 to 54	6.18e-10
			BBOX	87 to 128	9.80e-13
			PRY	286 to 338	4.07e-28
			SPRY	339 to 446	8.29e-44
20.	74748376	Q6AZZ1.1	RING domain	16 to 60	5.30e-09
			BBOX	93 to 134	5.30e-09
			PRY	302 to 354	7.37e-26
			SPRY	355 to 482	1.81e-26

Table 4: Domain Prediction of SSB/Anti-La (Sjogren's syndrome)

S. No	AC No. (NCBI)	Sequence Name	Domain	Sequence Position	E-Value
1.	62822319	AAY14868.1	LA	11 to 92	3.10e-42
2. 3. 4. 5. 6. 7. 10. 11. 12. 28.	10835067 178687 197692403 197692157 119631664 119631663 18089160 12654891 125985 32880067	NP_003133.1 AAA51885.1 BAG70165.1 BAG70042.1 EAX11259.1 EAX11258.1 AAH20818.1 AAH01289.1 P05455.2 AAP88864.1	RRM	112 to 183	5.09e-07
8.	|119631662	EAX11257.1	RRM-3 super family	94 to 190	9e-20
9.	119631661	EAX11256.1	LA	1 to 41	2.19e-03
			RRM	61 to 132	5.09e-07
13.	239775553	ACS15383.1	MHC II beta	8 to 82	4.33e-47
14.	198385574	ACH86118.1	MHC I Superfamily	1 to 178	7e-92
15. 16.	171904059 171904057	ACB56638.1 ACB56637.1	MHC I Superfamily	1 to 178	8e-93
17.	171903811	ACB56575.1	MHC I Superfamily	1 to 178	3e-93
18.	171903809	ACB56574.1	IGc	183 to 273	1e-18
			MHC Class I An alpha 1, 2	1 to 178	2e-87
19.	1732423	AAB51328.1	SPRY	86 to 220	1.19e-26
20.	86651712	ABD14426.1	La domain	13 to 48	1e-12
21.	88191928	|1ZH5	La	12 to 93	3.91e-39
22. 23. 24.	88191927 88191896 88191895	1ZH5 |1YTY 1YTY	RRM	113 to 184	8.73e-06
25.	108796061	NP_001035829.1	TROVE domain	1 to 94	2e-25
			vWFA	97 to 214	0.001
26.	108796056	NP_001035828.1	TROVE domain	18 to 369	1e-119
			vWFA	372 to 489	4e-04
27.	31377800	NP_004591.2	TROVE domain	18 to 369	7e-121
			vWFA	372 to 489	5e-04

ensemble approach to improve residue-residue contact prediction. A number of structural models stemming from a variety of methods and implementations. The various models capture slightly different conformations and contain complementary information which can be pooled together to capture recurrent, and therefore more likely, residue-residue contacts. (Ref 6)

Protein simulation is a post-translational modification that plays an important role in a wide range of cellular processes. Small ubiquitin-related modifier (SUMO) can be covalently and reversibly conjugated to the simulation sites of target proteins, many of which are implicated in various human genetic disorders. (Ref 7)

Methodology

Protein function prediction uses a single source of information the most common being the amino acid sequence of the protein. Biological databases can be used to retrieve the Gene sequences and Protein sequences. The protein sequences for Rheumatoid factor, SSA, SSB are retrieved from NCBI database. All these entries are relevant to the specific disease either the Rheumatoid arthritis or Sjogren's syndrome for Human species. Domains are the fundamental units of protein function which is predicted by the SMART (A Simple Modular Architecture Research Tool). It allows the identification and annotation of genetically mobile domains and the analysis of domain architectures. More than 500 domain families found in signaling, extra cellular and chromatin-associated proteins are detectable. These domains are extensively annotated with respect to phyletic distributions, functional class, tertiary structures and functionally important residues. Each domain found in a non-redundant protein database as well as search parameters and taxonomic information are stored in a relational database system.

Results and Discussion

The collected protein sequences from NCBI which represents the Rheumatoid factor those involved in Sjogren's syndrome (Human). Here we have done the sequence (100%) based domain prediction. From the collected and computed data we have observed that the Immunoglobulin domain (IGv) is mainly present in all those sequences. On the basis of E-value we already stated IGv domain is highly conserved from the position 1 to 67 (Table 1).

The Protein sequences represent the Rheumatoid factor those involved in Rheumatoid arthritis (Human). These observations (Table 2) suggests that based upon the predicted values IGv domain is predominantly present in all those sequences and slightly IGc1 domain and IG like domain is also present. On the basis of lower E-value IGv domain is highly conserved in the sequence, from position 17 to 98, and IGc1 domain from 147 to 220.

The gathered protein sequences represent the SSA proteins those involved in Sjogren's syndrome (Human). The predicted values shown in Table 3. Each sequence has differently contains CCP (Complementary control proteins), EGF (Epidermal

Growth Factor), EGFCA, VWA (Von Wille Brand type A domain), IG, IGc2, TSP1, TROVE, Calireticulin family, RING domain, BBOX, PRY, SPRY with different E-value. Furthermore, on the basis of lower E-value CCP (81-134), EGF (139-172), EGFCA(5315-5355), TROVE(18-369), IGc2(624-688), IGv(18-98), vWFA(97-214), SPRY(355-482) domains are highly conserved.

Table 4 shows that the SSB proteins those involved in Sjogren's syndrome (Human). These observations suggests that based upon the predicted values each sequence has differently contains La, RRM (RNA Recognition Motif), RRM-3 super family, MHC II beta, MHC I Super family, IGc, MHC Class I Antigen Alpha 1, 2 domain, SPRY, TROVE, vWFA along with various E-values. We have concluded that on the basis of lower E-value vWFA(97-214), TROVE(18-369), IGc(183-273), SPRY(86-220), La(13-48), MHC Class I An alpha 1, 2 (1-178) these listed domains are highly conserved.

Conclusion

From this work, we have observed that the Immunoglobulin domain (IGv) is mainly present in all those sequences. These observations also suggests that the predicted values of IGv domain is predominantly present in all those sequences and slightly IGc1 domain and IG like domain is also present. On the basis of lower E-value IGv domain is highly conserved in the sequence, from position 17 to 98, and IGc1 domain from 147 to 220.Each sequence has consist of varied composition of CCP (Complementary control proteins), EGF (Epidermal Growth Factor), EGFCA, VWA (Von Wille Brand type A domain), IG, IGc2, TSP1, TROVE, Calireticulin family, RING domain, BBOX, PRY, SPRY with different E-value. Finally, We have concluded that on the basis of lower E-value vWFA(97-214), TROVE(18-369), IGc(183-273), SPRY(86-220), La(13-48), MHC Class I An alpha 1, 2 (1-178) these listed domains are highly conserved.

References

1. Yanagisawa N, Haruta I, Kikuchi K, Shibata N, Yagi J Dysregulated inflammatory responses to commensal bacteria involved in the pathogenesis of hepatobiliary-pancreatic autoimmune disease. ISRN Gastroenterol. 2011:513514. (2011)
2. Woodrick RS, Ruderman EM; Medscape. Safety of biologic therapy in rheumatoid arthritis Nat Rev Rheumatol. 20 (32).145. (2011)
3. Rispens T, de Vrieze H, de Groot E, Wouters D, Stapel S, Wolbink GJ, Aarden LA Antibodies to constant domains of therapeutic monoclonal antibodies: Anti-hinge antibodies in immunogenicity testing. immunol Methods. 80 (4), 123 -132. (2011)
4. Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD, Tanasescu R Extra-articular Manifestations in Rheumatoid Arthritis. Maedica (Buchar).5(4):286-91. (2010)
5. Rajput R, Sehgal A, Jain D, Sen R, Saini O. Nephrocalcinosis: a rare presenting manifestation of primary Sjögren's syndrome. Mod Rheumatol. 45(12), 54. (2011)
6. Eickholt J, Wang Z, Cheng J. A conformation ensemble approach to protein residue-residue contact prediction. BMC Struct Biol. 12;11(1):38. (2011)
7. Teng S, Luo H, Wang L. Predicting protein simulation sites from sequence features. Amino Acids. (2011).