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International Journal of Current Research
Vol. 3, Issue, 11, pp.312-316, October, 2011

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

COMPARATIVE *INSILICO* STUDIES ON DOMAIN PREDICTION OF RHEUMATOID FACTORS IN RHEUMATOID ARTHRITIS AND SJOGREN'S SYNDROME

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ARTICLE INFO

Article History:
Received 12th May, 2011
Received in revised form
28th July, 2011
Accepted 7th September, 2011
Published online 30th October, 2011

Key words:
Antissa
Antissb
vWFA
TROVE
SPRY
Gv
IGc1
IG

ABSTRACT

Background: Autoimmune disorders are affect our own body cells by destroying organs, tissues and cells, yet the reason is unknown. Since the causative factor for autoimmune disoreder is questionable. The numerous autoimmune disoreders are available, all those are associated with one another by sharing symptoms, diagnosis and treatment. The affected body part also more or less similar. Among these, Rheumatoid arthritis and sjogrens syndrome receives more attention and turns the whole physician's concentrations to that side. Because the peoples those who have affected by RA are more susceptible to SS and vice versa. The principle behind that the common agent RF is involved in both diseases. In addition to this antiSSA and antiSSB are mostly involved in sjogren's syndrome.

Aim: To predict the common domains of rheumatoid factors (both rheumatoid arthritis and sjogren's syndrome) and antiSSA, antiSSB using computational tools.

Methods: Domains have been predicted for each factor using insilico tools and the sequence positions are displayed with the respective E-value.

Results: From these predictions, we have concluded that IGv domain of rheumatoid factor is majorly involved in both rheumatoid arthritis and Sjogren's syndrome. The prediction of antiSSA and antiSSB shows that vWFA, TROVE, and SPRY are the common domains involved only in sjogren's syndrome. But IGv, IGc1, and IG are the common domains mainly present in rheumatoid arthritis as well as Sjogren's syndrome.

Conclusions: The people's those who suffered by rheumatoid arthiritis having more number of chances to get sjogren's symdrome too. Because the domain IGv is commonly present in the rheumatoid factor of rheumatoid arthiritis and sjogren's syndrome.

Future Directions: By predicting this domain we can detect the malfunction or mutation, and onset of disease occurs, and model them as potential drug targets and propose the development of a common drug to tackle the disorder.

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 (Rose and Mackay, 1998). 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. In contrast to classical inherited genetic diseases, like sickle cell anemia, autoimmune diseases are not caused by the defect of a single gene, but by the dysfunction of the complex interaction of a group of genes (Hal Scofield, 2004; Peter C. Taylor, 2005; Andrew P. Cope, 2008; http://www.rheumatology.org).

Rheumatoid Arthritis

Rheumatoid arthritis is an autoimmune disease which normally helps protect the body from infection and disease, attacks joint tissues in a symmetric pattern for unknown reasons (Feldmann, 2001). Although the cause of rheumatoid arthritis is unknown autoimmunity plays a pivotal role in its chronic inflammation and progression. Rheumatoid arthritis causes joint destruction and thus often leads to considerable morbidity and mortality. Scientists have discovered that certain genes known to play a role in the immune system are associated with a tendency to develop rheumatoid arthritis. More than one gene is involved in determining whether a person develops rheumatoid arthritis and how severe the disease will become. A genetic link with HLA-DR4 and related allotypes of MHC Class II and the T cell-associated protein PTPN22. The presence of auto antibodies to IgG Fc, known as rheumatoid factors (RF), and antibodies to citrullinated peptides (ACPA) (Gioud-Paquet *et al.,* 1987).

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Rheumatoid Factor

Rheumatoid factor is most relevant in rheumatoid arthritis. It is an antibody against the Fc portion of IgG (Schrohenloher, 1988) which is itself an antibody. Rheumatoid factor and IgG join to form immune complexes which contribute to the disease process (Newkirk, 2002). Not all people with rheumatoid arthritis have detectable rheumatoid factor (Westwood *et al.,* 2006). Rheumatoid factor is also seen in other illnesses. For example Sjogren's syndrome, and in approximately 10% of the healthy population, therefore the test is not very specific. But rheumatoid factor may be detected in some healthy people, and people with autoimmune diseases sometimes have normal levels of rheumatoid factor.

Sjogren's Syndrome

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. In the case of Sjogren's syndrome, disease fighting cells attack various organs, most notably the glands that produce tears and saliva. Damage to these glands causes a reduction in both the quantity and quality of their secretions. This may cause the symptoms which include dry eyes and dry mouth. Sjogren's syndrome is classified as either primary (Gran and Myklebust, 2001) or secondary. Both are systemic diseases, meaning they can affect many systems in the body, and they occur with about equal frequency. The Primary form causes early and gradually progressive decreased function in the lachrymal and salivary glands, and can include a variety of extra glandular conditions. The Secondary form occurs in people who already have another autoimmune connective tissue disease, most commonly rheumatoid arthritis. This type of Sjogren's syndrome also called a rheumatic disease. This causes inflammation in joints, muscles, skin, and other organs. Like rheumatoid arthritis, it is also considered one of the autoimmune connective tissue diseases. These conditions affects joints, muscles, and skin. Rheumatoid Factor is positive in 90 percent of Sjogren's syndrome cases. Some people with Sjogren's syndrome have certain auto antibodies (Miyawaki, 1995) circulating in their blood called anti SSA (Montecucco *et al.,* 1989) and anti SSB (Hansen and Manthorpe, 1986; Moutsopoulos and Zerva, 1990). They are strongly but not exclusively associated with Sjogren's syndrome. Peoples with SSA/Anti-Ro and SSB/Anti-La are susceptible to Rheumatoid arthritis (Lee *et al.,* 1985; Franceschini *et al.,* 2003).

Domain Prediction

A protein consists of one or multiple domains, where a *domain* is defined as a region within a protein that either performs a specific function or constitutes a stable structural unit. A protein consists of one or multiple domains, where a *domain* is defined as a region within a protein that either performs a specific function or constitutes a stable structural unit. The combination of domains determines the function of the protein, its subcellular localization and the interactions it is involved in. Determining the domain structure of a protein is important for multiple reasons, including protein function analysis and structure prediction (Ingolfsson and Yona, 2008). Conserved domains might include a pattern of amino acids typical of a particular catalytic site or perhaps the binding site for a regulator of a protein. Since the domain is the binding site or active site, identification of the domain acts as the potential drug target and plays a vital role in drug discovery process. They are important for protein-to-protein interactions in processes of cell adhesion, cell activation, and molecular recognition. These domains are commonly found in molecules with roles in the immune system.

MATERIALS AND METHODS

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 (www.ncbi.nlm.nih/). All these entries are relevant to the specific disease either the Rheumatoid arthritis or Sjogren's syndrome for Human species. *In silico* analysis was performed using the biocomputing tool SMART (A Simple Modular Architecture Research Tool) available online at http://smart.embl-heidelberg.de/. 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 (Schultz *et al.,* 1998; Letunic *et al.,* 2009).

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.

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

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

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

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 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, (Hennig *et al.,* 2008) 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 involved in Sjogren's syndrome (Human). These observations suggests

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

S. No	AC No. (NCBI)	Sequence Name	Domain	Sequence Position	E-Value
1.	189491647|	NP_001121637.1	CCP	81 to 134	1.14e-14
2.	189491645	NP_694946.2	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	142 to 200	1.10e-07
			protein)	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.	4757900	NP_004334.1	Calreticulin family	22 to 332	6e-121
23.	4757900	|NP_004334.1			
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.	747927	AAA79867.1	RING domain	16 to 54	6.18e-10
19.	337485	AAA36581.1	BBOX	87 to 128	9.80e-13
21.	133250	P19474.1	PRY	286 to 338	4.07e-28
22.	15208660	NP_003132.2	SPRY	339 to 446	8.29e-44
24.	14790039	AAH10861.1			
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.	10835067	NP_003133.1			
3.	178687	AAA51885.1	RRM	112 to 183	5.09e-07
4.	197692403	BAG70165.1			
5.	197692157	BAG70042.1			
6.	119631664	EAX11259.1			
7.	119631663	EAX11258.1			
10.	18089160 12654891	AAH20818.1			
11.	125985	AAH01289.1			
12.	32880067	P05455.2			
28.		AAP88864.1			
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.	171904059	ACB56638.1	MHC I Superfamily	1 to 178	8e-93
16.	171904057	ACB56637.1			
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		12 to 93	3.91e-39
22.	88191927	1ZH5	La		
23.	88191896	|1YTY	RRM	113 to 184	8.73e-06
24.	88191895	1YTY			
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

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. On the basis of lower E-value, we have concluded that vWFA(97-214), TROVE(18-369), IGc(183-273), SPRY(86-220), La(13-48), MHC Class I An alpha 1, 2 (1-178) domains are highly conserved.

Conclusion

The Immunoglobulin domain (IGv) is mainly present in all the protein sequences of Rheumatoid factor, which is involved in Sjogren's syndrome. Meanwhile the predicted values for the protein sequences of rheumatoid factor, which is involved in rheumatoid arthritis, show that 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 all the protein sequences of rheumatoid factor (Schrohenloher, 1988). From these predictions, we have concluded that IGv domain of rheumatoid factor is majorly involved in both rheumatoid arthritis and Sjogren's syndrome. The domain prediction of SSA/Anti-Ro, involved in Sjogren's syndrome (Moutsopoulos and Zerva, 1990), shows that each sequence has consist of varied compositions of CCP (Complementary control proteins), EGF (Epidermal Growth Factor), EGFCA, VWA (Von Wille Brand type A domain), IG, IGc2, TSP1, TROVE, IGv, Calireticulin family, RING domain, IGc1, BBOX, PRY, SPRY with different E-value. It shows that IGv, IGc1, and IG are the common domains mainly present in rheumatoid arthritis as well as Sjogren's syndrome. The prediction of SSB/Anti-La (Moutsopoulos and Zerva, 1990) shows that each sequence has differently contains the highly conserved domains such as vWFA, TROVE, IGc, SPRY, La, RRM, MHC Class I An alpha 1, 2. It shows that vWFA, TROVE, and SPRY are the common domains involved only in sjogren's syndrome with the association of SSA/Anti-Ro, but the IGc domain is present in SSA/Anti-Ro, SSB/Anti-La, and rheumatoid factor of rheumatoid arthritis.

From these computational studies, we have observed that rheumatoid arthritis and sjogren's syndrome is mostly linked with one another. The people's those who suffered by rheumatoid arthiritis having more number of chances to get sjogren's symdrome too. Because the domain IGv is commonly present in the rheumatoid factor of rheumatoid arthiritis and sjogren's syndrome and SSA/Anti-Ro. Additionally, the people's with sjogren's syndrome is more susceptible to have rheumatoid arthritis (Lee *et al.,* 1985). As described above, IGc is the major domain present in SSA/Anti-Ro (Franceschini *et al.,* 2003), SSB/Anti-La, and rheumatoid factor of rheumatoid arthritis, it connects the rheumatoid arthritis and sjogren's syndrome (Montecucco *et al.,* 1989). Whereas the domains vWFA, TROVE, and SPRY are majorly present in SSA/Anti-Ro, SSB/Anti-La and involved only in sjogren's syndrome, not associated with rheumatoid arthritis. Furthermore, When the peoples having IGv domain, especially the sequence position from 1 to 66, 3 to 75, 17 to 98, 10 to 91, 18 to 90, and 18 to 91 and IGc domain, the sequence position 222 to 293, 183 to 273 must getting more number of chances to suffer by both rheumatoid arthritis as well as sjogren's syndrome or either one of the diseases probably. So, further studies are required to identify how these domains are involved in diseases and interacted with each other. More investigations are needed to predict the drug based upon the above-mentioned sequence position to arrest the disease in molecular level itself as well as embryonically.

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