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Full Length Research Paper

In-silico analysis of *Mycobacterium leprae* genome to find out potential drug targets

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***Mycobacterium leprae* is the causative agent of the disease, leprosy. In-silico analysis can be performed on *M. leprae* genome to find out the potential drug targets. This was done first by database search to find the recorded complete genes with complete sequences of *M. leprae* and then their comparative study with human by using homology searching using human BLAST. From a total of 1605 genes, potential drug targets have been identified.**

Key words: *Mycobacterium leprae* Genome, BLAST, NCBI, drug target

INTRODUCTION

Leprosy remains an important health problem world (Britton and Lockwood, 2004). At the beginning of 2004, the number of leprosy patients under treatment in the world was around 460,000. About 515,000 new cases were detected during 2003 (WHO, Leprosy Elimination Group, 2004). Among them, 43% were multibacillary cases. 12% were children, and 5% diagnosed with severe disabilities (WHO, Leprosy Elimination Group, 2004). *Mycobacterium leprae* is the causative agent of the disease, leprosy, also known as Hanson's Disease. The bacterium was discovered in 1873 by a Norwegian physician named Gerhard Armauer Hansen (Luis Fernandez et al., 2004). *M. leprae* is a gram-positive, aerobic rod surrounded by the characteristic waxy coating unique to Mycobacteria. In size and shape, it closes resembles *M. tuberculosis*. Leprosy has afflicted humanity since time immemorial. It once affected every continent and it has left behind a terrifying image in history and human memory - of mutilation, rejection and exclusion from society. An important problem in the control of leprosy is drug resistance (Mistry and Antia, 1993; Williams and Gillis, 2004). Newer molecular approaches, including the polymerase chain reaction (PCR), may be more useful and it will be important to undertake studies to develop such tools (Gupta and Katoch, 1999) . The use of advanced molecular biology technology to discover new drugs to treat resistant organisms is needed.

The need for tools to rapidly identify drug targets

The cost of research and development in the pharma-ceutical industry has been rising steeply and steadily in the last decade, but the amount of time required to bring a new product to market remains around ten to fifteen years (Humer, 2005). This problem has been labeled an ‘‘innovation gap,’’ and it necessitates investment in inexpensive technologies that shorten the length of time spent in drug discovery. The target identification stage is the first step in the drug discovery process (Terstappen GC and Reggiani A, 2001) and as such can provide the foundation for years of dedicated research in the pharmaceutical industry. As with all the other steps in

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drug discovery, this stage is complicated by the fact that the identified drug target must satisfy a variety of criteria to permit progression to the next stage. Important factors in this context include homology between target and host (to prevent host toxicity such homology must be low or nonexistent (Freiberg, 2001) activity of the target in the diseased state (Wang et al., 2004) and the essentiality of the target to the pathogen's growth and survival. The values of some of these selection criteria can be found easily by querying publicly available bioinformatics resources, including metabolic pathway databases such as KEGG (Kyoto encyclopedia of genes and genomes), NCBI (National Center for Biotechnology Information) for retrieving complete genome of any organism, and databases of 'druggable'' (potentially useful as drug targets) proteins (Sanseau, 2001).

MATERIALS AND METHODS

Searching for the *M. leprae complete* genes

Complete genes of *M. leprae* can identify by database searching method. We had used National Center for Biotechnology Information (www.ncbi.nlm.nih.gov) for identifying all gene sets.

Comparative analysis with human

The identified genes from *M. laprae* genome were compared with human genes in order to find out drug target genes. Using Basic Local Alignment Search Tool (human BLAST) (McGinnis and Madden, 2004) did comparative study. Genes which lack the homology with human was considered as potential drug target candidates for further drug development process.

Finding the functions shown by the targets

The obtained targets were further taken and scan by uniprot (www.uniprot.org) database to find out their functions (Table 2).

RESULTS

After database search we have found total 1605 genes in the *M. laprae* genome, we had annotated all the genes and removed all hypothetical genes to refine the results. After removing all hypothetical genes, 805 genes have been derived for further analysis. Out of these 805 genes, 126 genes (Table 1) were found to lack significant homologues to the human genome and were identified as potential candidates for further target based drug development. After comparative study with human, we have found genes with or without homologue to human. Genes those were homologous to human were neglected as they were functionally similar with those of human and as a drug, they can led to unwanted toxicity. However on the other hand, there were 126 genes found by human BLAST homology searching method that were showing no similarity with human. These genes can work for future drug discovery process.

DISCUSSION

According to the World Health Organization (WHO), the global registered prevalence of leprosy at the beginning of 2008 stood at 212,802 cases, while the number of new cases detected during 2007 was 254,525 (Mary Kugler R.N., About.com, 2009).

Since 1940, treatment using dapsone has been used to suppress leprosy (WHO, Leprosy Elimination Group, 2004). Seldom can leprosy be completely eradicated from a patient's skin and tissues; modest expectations for newer and better drug combinations led to MDT for the control of leprosy (Noordeen, 2000; WHO, Leprosy Elimination Group, 2004).

Since it is generally believed that the genomes of bacteria contain both genes with and without homologues to the human host. Using in silico approach for drug targets target identification is very quick to produce a desirable list.

Here we performed database search and found total 1605 genes in the *M. laprae* genome, we had annotated all the genes and removed all hypothetical genes to refine the results. After removing all hypothetical genes, 805 genes have been derived for drug target selection.

Conclusion

Our research provides a simple framework for integrating the vast amount of genomic data that can be used in the drug target identification stage. Drugs that specifically target genes with high homology to the host can lead to unwanted toxicity, therefore, finding new antileprosy drugs should based on genome homology.

We were able to predict about 126 genes (Table 1) out 1605 protein coding genes of *M. leprae* genome. These 126 genes were found to lack significant homologues to the human genome. However on the other hand there were 126 genes found by human BLAST homology searching Method (Thammarongtham and Palittapongarnpim, 2002) that were showing no similarity with human. These genes can work for future drug discovery process.

Table 2 shows some targets involved in some important functions. Of these 6 candidate targets are involved in cell wall biosynthesis, 11 targets involves in ATP binding. It has been noted, however, the drugs that target cell wall synthesis are more likely to be active against growing bacteria. Also we have found 2 antibiotic resistance target and 5 target are involved in folate biosynthesis, which are interesting and important pathway to target for drug development.

Table 1. *Mycobacterium leprae* potential drug target genes with Gene ID.

S. No	Gene Id	Drug Target genes	Similarity with human
1	908143	dnaA	Nil
2	908144	dnaN	Nil
3	910311	rodA	Nil
4	908231	menG	Nil
5	908182	hns	Nil
6	910395	pheA	Nil
7	908335	embB	Nil
8	908337	embA	Nil
9	908339	embC	Nil
10	908361	rfbE	Nil
11	908384	lipE	Nil
12	908436	fadD29	Nil
13	908464	lppX	Nil
14	908466	mmpL7	Nil
15	908505	uvrD	Nil
16	908560	mscL	Nil
17	908570	rimJ	Nil
18	908646	folP	Nil
19	908411	folB	Nil
20	908689	folK	Nil
21	908653	panC	Nil
22	908703	pabB	Nil
23	908726	rplY	Nil
24	908727	lpqT	Nil
25	908850	thiG	Nil
26	908861	thiE	Nil
27	908869	glnH	Nil
28	909217	pssA	Nil
29	909986	lpqE	Nil
30	908920	ispF	Nil
31	909060	alr	Nil
32	909169	lppS	Nil
33	909202	pgsA	Nil
34	909213	dedA	Nil
35	909230	ruvC	Nil
36	909231	ruvA	Nil
37	909239	yajC	Nil
38	909240	secD	Nil
39	909241	secF	Nil
40	909272	aroE	Nil
41	909276	aroD	Nil
42	909283	nusB	Nil
43	909285	adi	Nil
44	909117	pyrF	Nil
45	909302	PE	Nil
46	909303	PPE	Nil
47	909319	priA	Nil
48	909336	ribC	Nil
49	909338	ribA	Nil
50	909360	ppc	Nil
51	910135	tal	Nil
52	909396	subI	Nil
53	910360	mtb12	Nil
54	909420	uvrD2	Nil
55	909422	whiB7	Nil
56	909655	ftsX	Nil
57	910083	smpB	Nil
58	909593	sdhD	Nil
59	909683	purK	Nil
60	909681	purE	Nil
61	909766	entC	Nil
62	909792	dnaG	Nil
63	909803	cysE	Nil
64	909819	narK	Nil
65	098629	cobT	Nil
66	909885	trpD	Nil
67	909902	murE	Nil
68	909915	murF	Nil
69	909911	murD	Nil
70	909914	ftsW	Nil
71	909917	murG	Nil
72	909916	murC	Nil
73	909922	ag84	Nil
74	909964	ppdK	Nil
75	909974	metE	Nil
76	909997	ftsK	Nil
77	910283	recX	Nil
78	910020	dapF	Nil
79	910085	ppgK	Nil
80	910461	tagA	Nil
81	910163	sigE	Nil
82	910225	thrB	Nil
83	910324	lspA	Nil
84	910322	bioD	Nil
85	910333	nadA	Nil
86	910337	papA3	Nil
87	910336	mmpL10	Nil
88	910348	hisB	Nil

Table 1. Cont.

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89	910370	hisI	Nil
90	910382	trpC	Nil
91	910528	rpmI	Nil
92	910543	pheT	Nil
93	910547	argB	Nil
94	909482	nadD	Nil
95	909495	rplU	Nil
96	909506	mmuM	Nil
97	909509	Tig	Nil
98	909521	fdxA	Nil
99	910150	folP2	Nil
100	910233	atpF	Nil
101	910413	uppP	Nil
102	910454	tatA	Nil
103	910487	tlyA	Nil
104	910489	recN	Nil
105	910501	cmk	Nil
106	910543	pheT	Nil
107	910545	argC	Nil
108	910546	argJ	Nil
109	910553	argR	Nil
110	909820	rimM	Nil
111	909837	glnE	Nil
112	910042	thiL	Nil
113	910044	ddl	Nil
114	910764	fecB	Nil
115	910758	nrdI	Nil
116	910738	sdaA	Nil
117	910722	uspE	Nil
118	910696	hsp18	Nil
119	910663	PPE	Nil
120	910651	sppA	Nil
121	910650	rplO	Nil
123	910632	rplV	Nil
124	908542	greA	Nil
125	908512	umaA2	Nil
126	908410	aac	Nil

Table 2. No. of target showing different functions.

Functions obtained from uniprot. www.uniprot.org	No. Targets Involved
ATP binding,	11
Antibiotic resistance	04
DNA binding	02
Biosynthetic process	06
Cell wall biosynthesis	06
Ribonuclease inhibitor activity	01
Metabolic process	03
Amino-acid biosynthesis	04
Transferase activity	04
Protein transport	02
Transcription regulation	02
Translation	03
Thiamine biosynthesis	03
DNA damageDNA recombination DNA repair	02
Folate biosynthesis	05
Phospholipid biosynthetic process	03
Hydrolase activity	01
Sugar transport	01
Iron ion transmembrane	01
Signal peptide processing	01
Electron carrier activity	01
Homocysteine S-methyltransferase activity	01

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