A computational framework to find novel therapeutics for autoimmunity

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Abstract
The immune system protects a host from foreign pathogens. In rare cases, the immune system can attack the cells of the host organism causing autoimmune diseases. We outline a computational framework that combines bioinformatics and network analysis with an emerging targets platform.
The computational framework presented here can be used to find drug targets for autoimmune diseases. It can also be used to find existing drugs that can be repurposed to treat autoimmune diseases based on networks of interactions or similarities between different diseases. Information on which gene regions are associated with the disease (single nucleotide polymorphisms) can be used in gene therapy when that technique becomes viable. Our analysis also revealed immune cell subtypes that are implicated in these diseases. These immune cell subtypes can be selected for immunotherapy experiments. Finally, our analysis also reveals intra-cellular and protein-protein interaction networks and pathways that can be targeted with small molecule inhibitors. The downstream off-target effects of these inhibitors can also be determined from such a network analysis. In summary, our computational framework can be used to find novel therapeutics for autoimmune diseases and potentially even other dysfunctions.

Keywords autoimmune diseases, bioinformatics, network analysis, immune system modelling, agent based models, ordinary differential equation models.

1 Introduction
The immune system is tasked with protecting a host from external pathogens. It is trained to not recognize self (peptides that are expressed by normal cells in the body of the host). However, in some cases it erroneously recognizes and attacks normal cells in the host. These are called autoimmune diseases.

Insights from bioinformatics coupled with data from emerging curated repositories can lead to novel therapeutics that may ameliorate symptoms of these diseases and help patients lead a normal lifestyle.

We use bioinformatics and network analysis techniques combined with an emerging drug targets platform. We use this approach to show how insights can be derived into potential drug targets of two autoimmune diseases: systemic lupus erythematosus and Sjogren disease. Our work shows the potential of combining computational techniques with emerging repositories to drive insights into the immune system in health and disease.

2 Methods

Our approach is to combine bioinformatics and network analysis approach with an emerging platform that has curated information on diseases and their drug targets. We use an emerging platform to quantify targets for an autoimmune disease (https://www.targetvalidation.org/) (Koscielny et al., 2017).

Our computational framework combines bioinformatics with network approaches along with a novel repository. Such an approach can enable search for new targets for diseases and insights into mechanisms. We show this approach here for autoimmune diseases. Our code is available for download from a repository (https://bitbucket.org/neelsoumya/autoimmune_targets_pipeline).

3 Results

3.1 Top targets associated with systemic lupus erythematosus

Querying the platform revealed that Interferon Regulatory Factor 5 (IRF5) is a top factor involved in systemic lupus erythematosus.

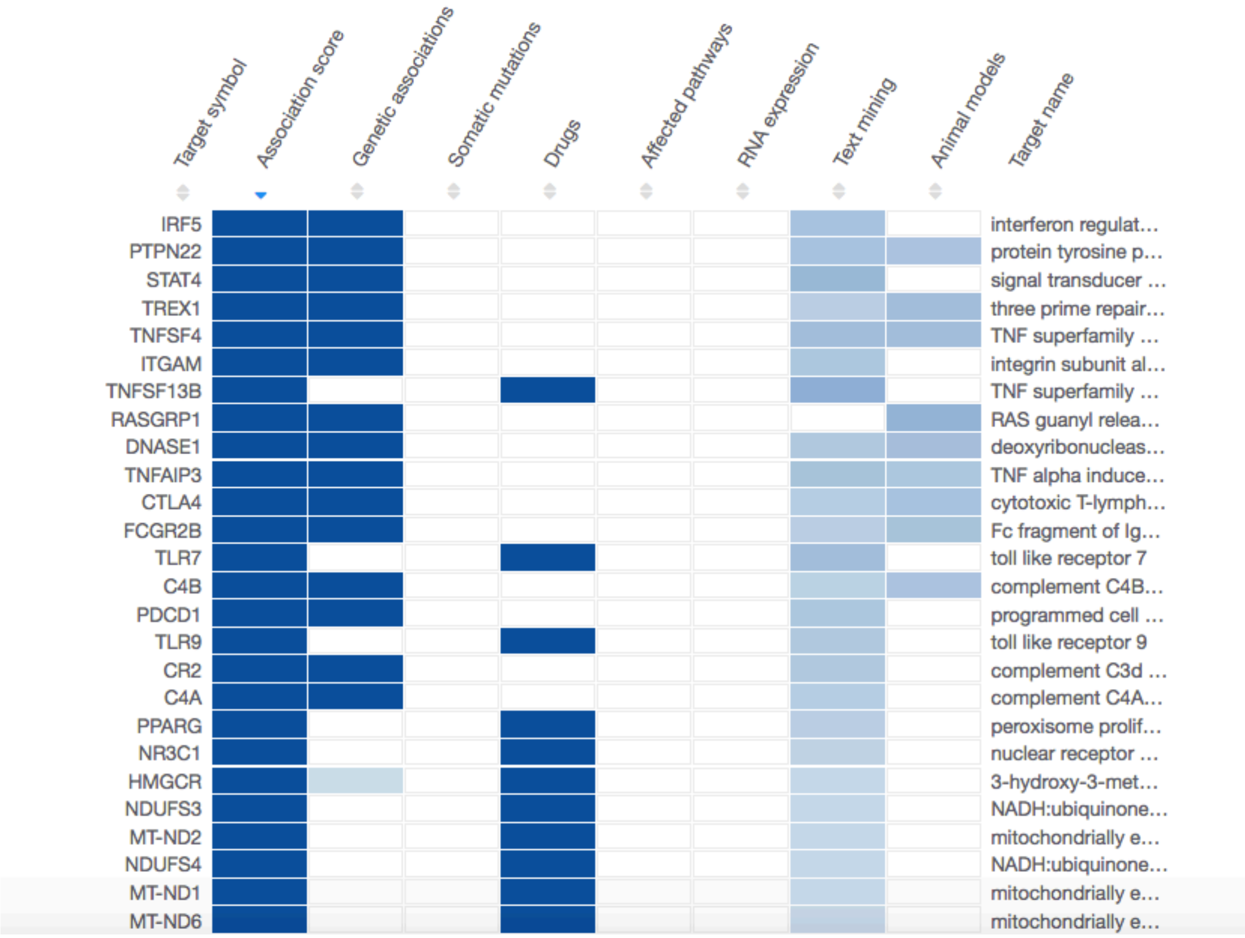

Figure 1. A depiction of the top targets for systemic lupus erythematosus. IRF5 is predicted to be a very important target along with other factors (available from https://www.targetvalidation.org/disease/EFO_0002690/associations and https://www.targetvalidation.org/disease/EFO_0002690).

Some of the known drugs in use or currently in testing for systemic lupus erythematosus are shown in Table 1. Most of the drugs are small molecule inhibitors. This kind of information can be used to find novel drug targets. A complete list is available in Supplementary Information.

Drug	Type	Mechanism of action
Dexamethasone	N/A	Small molecule
Dexamethasone	N/A	Small molecule
Metformin	Recruiting	Small molecule
Metformin	Recruiting	Small molecule
Pioglitazone	Completed	Small molecule
Dexamethasone Phosphoric Acid	N/A	Small molecule
Prednisolone	N/A	Small molecule
Prednisone	N/A	Small molecule
Metformin	Recruiting	Small molecule

Table 1. Known drugs in use or testing for systemic lupus erythematosus (complete list available in Supplementary Information).

3.2 IRF5 interaction network

We also constructed the network of interactions between interferon regulatory factor 5 (IRF5) and other factors (Fig. 2).

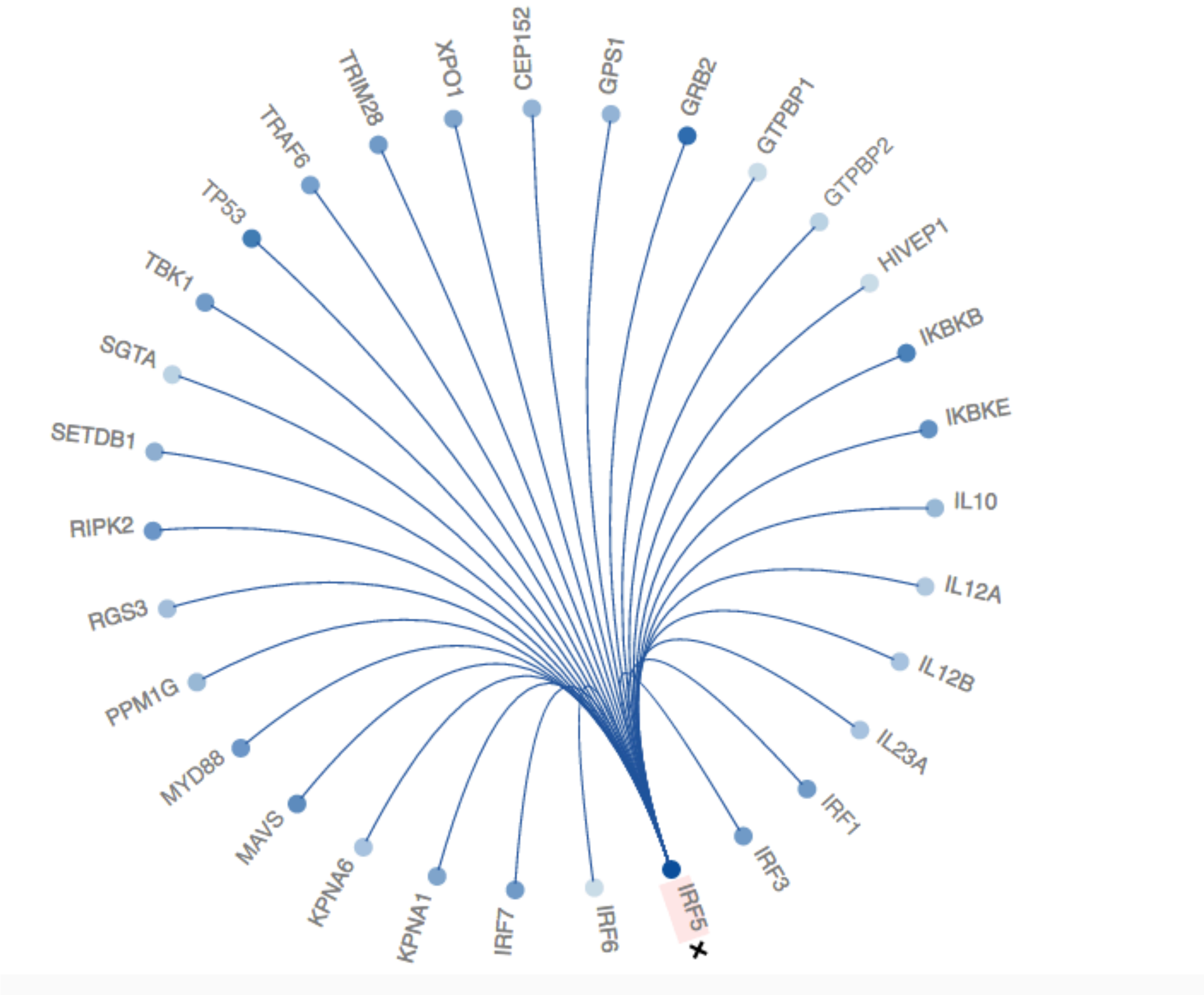

Figure 2. Network of interactions between Interferon regulatory factor 5 and other factors (available from https://www.targetvalidation.org/target/ENSG00000128604).

This kind of network of interactions with other factors can be used to find drug targets that can influence IRF5.

IRF5 is a very important factor that is also implicated in a host of other autoimmune diseases. We show the association of IRF5 with other diseases like rheumatoid arthritis and inflammatory bowel disease (Fig. 3).

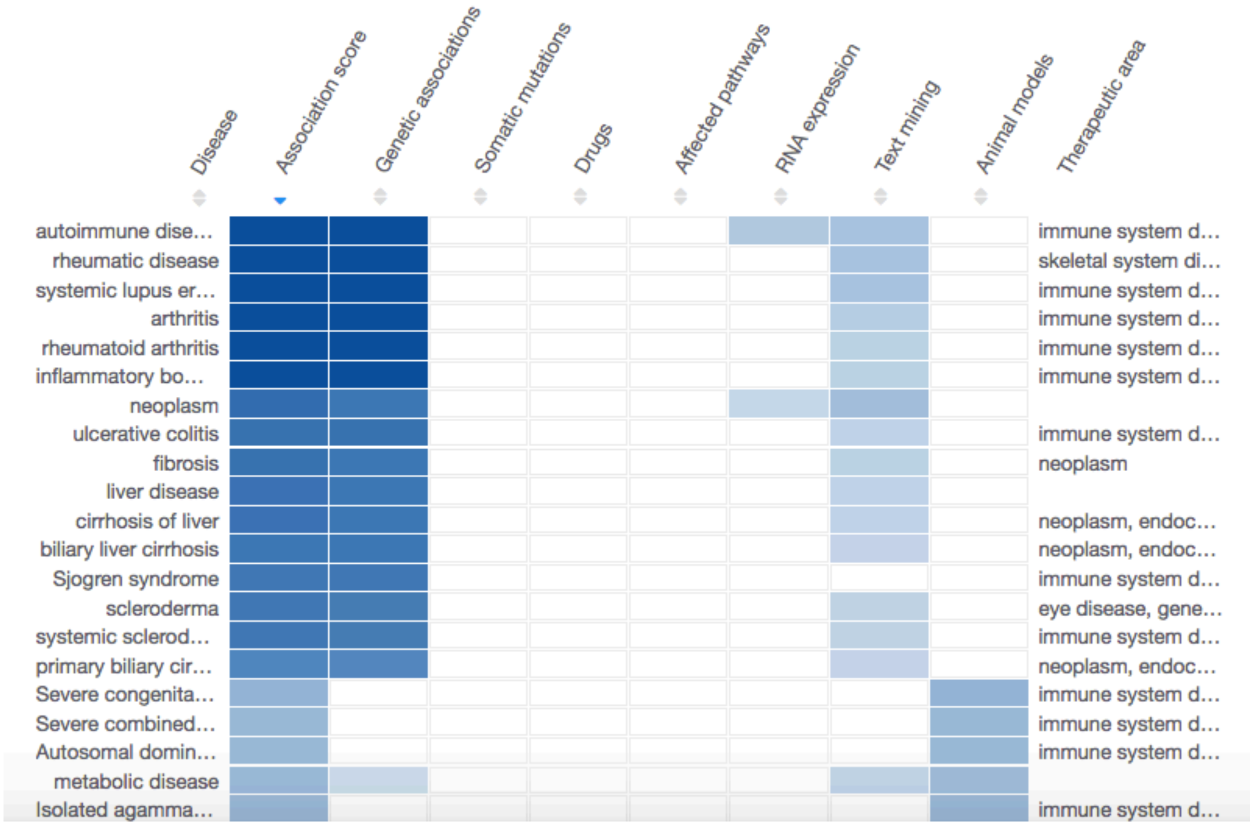

Figure 3. IRF5 is a very important factor that is also implicated in a host of other autoimmune diseases. The diseases are shown in this figure (available from https://www.targetvalidation.org/target/ENSG00000128604/associations?view=t:table).

3.3 Interactions with other diseases: Sjogren syndrome

We demonstrate our approach by using another autoimmune disease called Sjogren syndrome.
We look at the network of associations between other diseases and Sjogren syndrome (Fig. 4). This kind of information can be used to find existing drugs that can be repurposed to treat this disease.

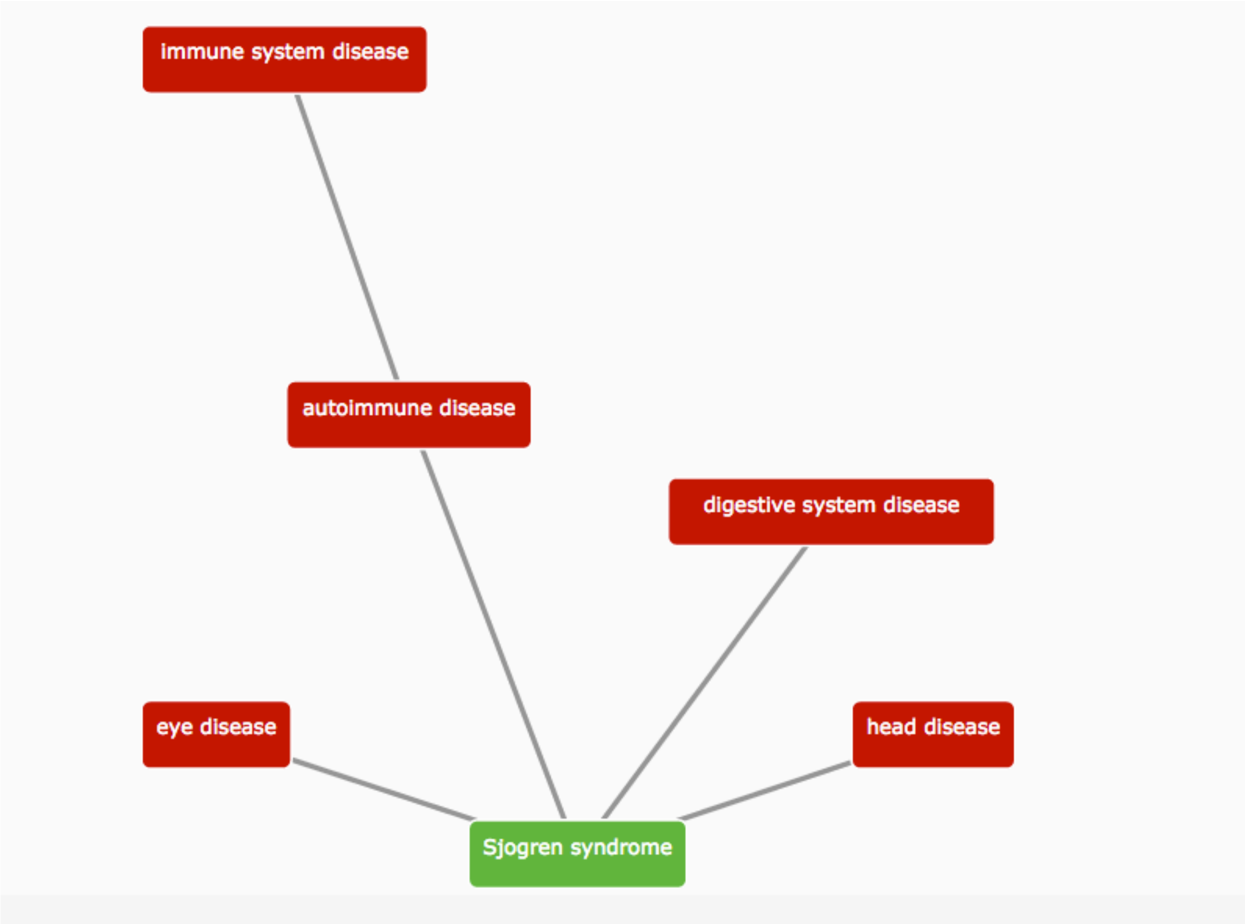

Figure 4. A network of associations between other diseases and Sjogren syndrome (available from https://www.targetvalidation.org/disease/EFO_0000699).

3.4 Targets and Associations

The associations of other diseases with Sjogren disorder are shown in Fig. 5.

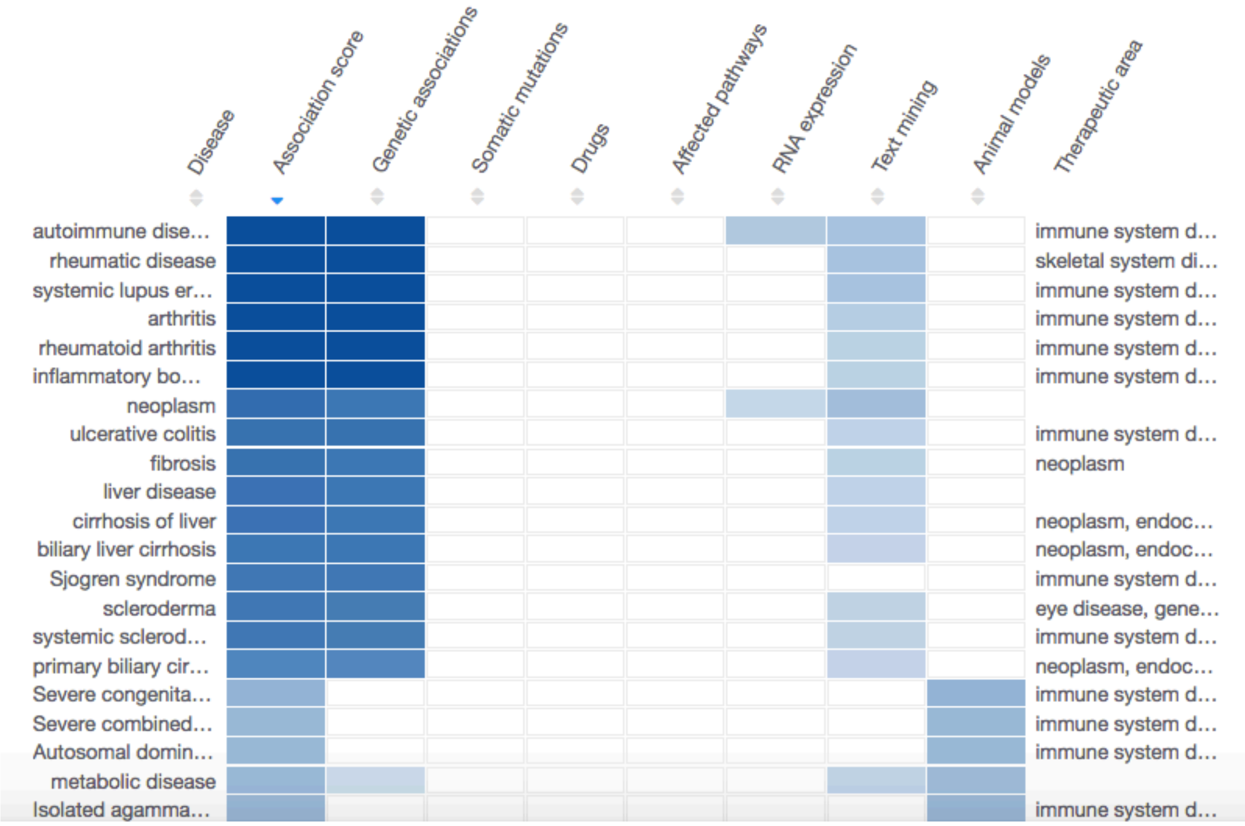

Figure 5. Associations of Sjogren disorder with other diseases (available from https://www.targetvalidation.org/disease/EFO_0000699/associations).

Some of the current drugs that are in use or development for Sjogren syndrome are also shown in Table 2.

Drug	Status	Type
Dexamethasone	Completed	Small molecule
Hydroxychloroquine	Completed	Small molecule
Hydroxychloroquine	Completed	Small molecule
Baminercept	Terminated	Protein
Mycophenolate Mofetil	Enrolling	Small molecule
Efalizumab	Terminated	Antibody
Belimumab	Completed	Antibody
Mycophenolate Mofetil	Completed	Small molecule
Baminercept	Terminated	Protein

Table 2. Drugs that are in development or use for Sjogren disorder.

3.5 IRF5 intra-cellular pathway and interaction network

We constructed the network of IRF5 intra-cellular pathway and interaction networks (Fig. 6). These network diagrams can be used to find more novel targets.

The network diagrams suggest there are key hubs. This can be used to find off-target effects or side effects of drugs by outlining key connections to other functions.

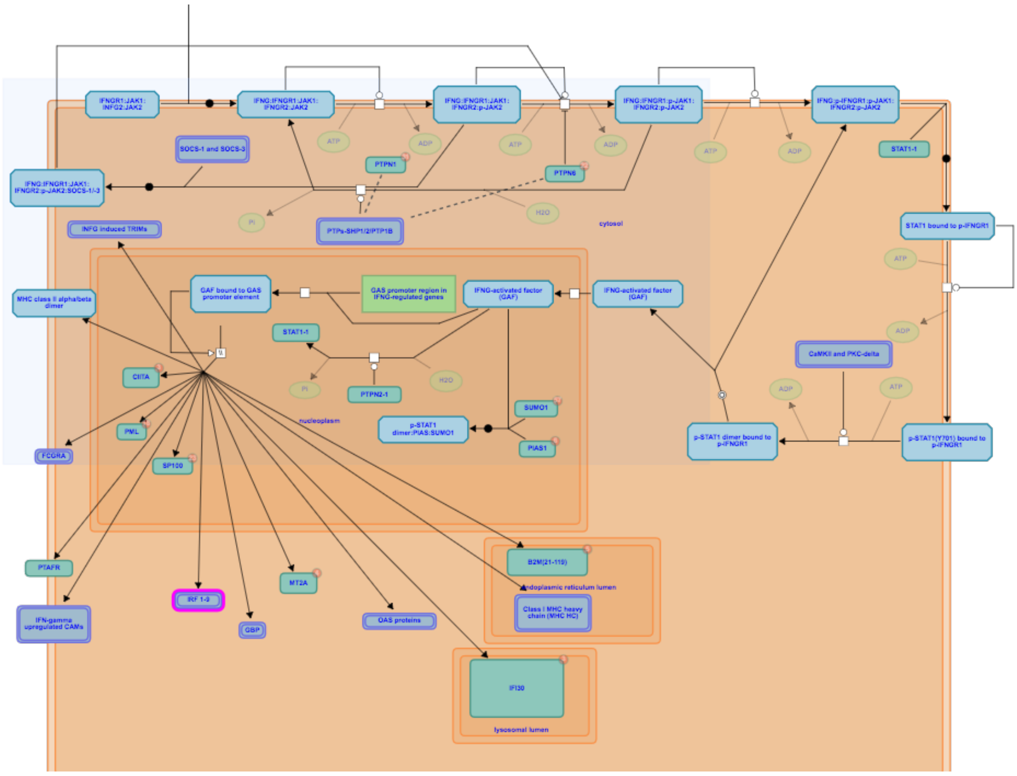

Figure 6. A network of IRF5 intra-cellular pathway and interaction networks.

3.6 Genes and single nucleotide polymorphisms associated with disease

Using the computational framework, we found single nucleotide polymorphisms (SNP) in genes associated with these diseases. One of these is rs2004640 which is a SNP in the IRF5 gene in the chromosomal region 7q32.1. This is associated with systemic lupus erythematosus. Some of the genes and transcript consequences are listed in Table 3. A full list is available online (see Supplementary Information; filename: Mappings-Homo_sapiens_Variation_ Mappings_ rs2004640_ consequences.csv).

Gene	Consequence Type
ENSG00000128604 HGNC: IRF5	splice donor variant
ENSG00000128604 HGNC: IRF5	intron variant
ENSG00000128604 HGNC: IRF5	intron variant
ENSG00000128604 HGNC: IRF5	intron variant non-coding transcript variant
ENSG00000128604 HGNC: IRF5	intron variant
ENSG00000128604 HGNC: IRF5	upstream gene variant
ENSG00000128604 HGNC: IRF5	upstream gene variant
ENSG00000128604 HGNC: IRF5	upstream gene variant
ENSG00000128604 HGNC: IRF5	intron variant NMD transcript variant

Table 3. Genes and transcript consequences for systemic lupus erythematosus (full list available at .http://www.ensembl.org/Homo_sapiens/Variation/Mappings?db=core;r=7:128937747-128938747;v=rs2004640;vdb=variation;vf=1430080)

Some of the transcripts with tissues where they are likely expressed in are listed in Table 4. A full list is available online (see Supplementary Information; filename: Mappings-Homo_ sapiens_ Variation_ Mappings_rs2004640.csv).

Gene	Effect size	Tissue
ENSG00000128594	0.00213	Adipose subcutaneous
ENSG00000135245	0.01738	Adipose subcutaneous
ENSG00000240758	0.01619	Adipose subcutaneous
ENSG00000128524	0.01906	Skin sun exposed lower leg
ENSG00000128594	-0.11824	Thyroid
ENSG00000230715	-0.02340	Adipose subcutaneous
ENSG00000243679	0.00280	Adipose subcutaneous
ENSG00000229413	-0.06162	Adipose subcutaneous
ENSG00000271553	-0.07070	Adipose subcutaneous

Table 4. Transcripts with tissues where they are likely expressed and effect size (for SNP in rs2004640).

We note that some of the genes (like ENSG00000128594) are associated with thyroid disease, which is observed in patients with systemic lupus erythematosus. Finally, one of the regulatory features (ENSR00000217801) is active in cell lines consisting of many immune system cells (like B cells, natural killer cells and macrophages), and normal cells like those found in the spleen and pancreas (full list available from Supplementary Information; filename: Mappings-Homo_ sapiens_ Variation_ Mappings_ rs2004640_ regulatory.csv). In the future, it may be possible to use therapeutics to specifically target these cells or sites.

4 Discussion

The immune system protects the host against foreign pathogens. In rare circumstances, it can harm cells of the host causing autoimmune diseases. We present a computational framework that combines bioinformatics and network analysis approaches with data from a novel platform. Our framework can be used to find novel therapeutic strategies for autoimmune diseases. We show this using two autoimmune diseases: systemic lupus erythematosus and Sjogren disorder.

The computational framework presented here can be used to find drug targets for autoimmune diseases. It can also be used to find existing drugs that can be repurposed to treat autoimmune diseases. For example, Sjogren is associated with other diseases (Fig. 5). Association information of this nature can be used to repurpose existing drugs to treat these diseases.

Information on which gene regions are associated with the disease (single nucleotide polymorphisms in Table 3) can be used in gene therapy when these techniques becomes viable.

Our analysis also reveals intra-cellular and protein-protein interaction networks and pathways that can be targeted with small molecule inhibitors. The downstream off-target effects of these inhibitors can also be determined from such a network analysis (intra-cellular regulatory network for IRF5, Fig. 6).

Our framework also revealed immune cell subtypes and specific sites that are implicated in these diseases (associated with a regulatory feature: ENSR00000217801). These immune cell subtypes can be selected for immunotherapy experiments. In the future, it may also be possible to use therapeutics to specifically target these sites instead of using systemic drugs.

Our approach can be combined with infectious disease models (Banerjee, 2013; Banerjee, 2015; Banerjee and Moses, 2010a; Banerjee et al., 2016). Population level approaches like ordinary differential equations are computationally tractable and can scale up to simulate host pathogen dynamics in large organisms (Banerjee and Moses, 2009). These can also be used to investigate the role of molecular mimicry in autoimmune diseases. Finally, hybrid modelling approaches can also be very useful in modelling these biological systems (Banerjee et al, 2015; Banerjee, 2015b, 2015c).

Our techniques can also be combined with data on auto-antibodies and design specific strategies to increase levels of certain classes of protective auto-reactive (immunoglobulin M) IgM antibodies (Fattal et al., 2010). Our framework can also be used to find classes of T-regulatory cells that have a protective function in autoimmune diseases (Herwijnen et al., 2012). Future work will also investigate linking drug target databases with curated repositories of natural substances such as polyphenol (found in green tea) that have also been known to recruit T-regulatory cells (Wong et al., 2011). This may lead to novel natural compounds that have a protective function in autoimmune diseases. Finally, our framework can be extended to incorporate information on idyotypic networks of antibodies (antibodies that link to other antibodies) that may have a role in autoimmune diseases (Shoenfeld, 2004).

In summary, we present a computational framework for combining bioinformatics with network approaches along with a novel repository can enable us to find new targets for diseases. We show this here for autoimmune diseases. Our code is freely available from a repository (https://bitbucket.org/neelsoumya/autoimmune_targets_pipeline). Computational techniques like these can shed light on the immune system in disease and help find novel therapeutic strategies.

Acknowledgment

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Supplementary Information

A full list of all drugs in use or development and single nucleotide polymorphisms for Sjogren disorder and systemic lupus erythematosus, along with all code is available online (https://bitbucket.org/neelsoumya/autoimmune_targets_pipeline).

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