Mining gene-disease associations with Open Targets

Webinar Coursebook

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Notes

This webinar is based on the December 2016 release of our Open Targets Platform.

Some useful links:

1) About the Open Targets Consortium
www.opentargets.org/about

2) About the Open Targets Platform
www.targetvalidation.org/about

3) Our publication
www.bit.ly/OpenTargets

4) Details on the latest Platform release
https://blog.opentargets.org/open-targets-platform-our-new-release-is-out-2/

Feel free to tackle questions relative to your own research instead of following the ones provided in this coursebook.

Questions or Feedback?
support@targetvalidation.org

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OVERVIEW

Open Targets is a public-private initiative to generate evidence on the validity of therapeutic targets based on genome-scale experiments and analysis. We are working to create an R&D framework that applies to a wide range of human diseases, and we want to share this data openly with the scientific community.

The consortium was launched in March 2014 under the name of Centre for Therapeutic Open Targets (CTTV) and started with GlaxoSmithKline (http://www.gsk.com/), the Wellcome Trust Sanger Institute (http://www.sanger.ac.uk/) and the European Bioinformatics Institute (http://www.ebi.ac.uk/). In February 2016, a forth institution namely Biogen (https://www.biogen.com/) joined the initiative and the consortium was rebranded to Open Targets in April 2016.

In the process of drug discovery, the *validation* of a target refers to the creation of a specific entity that modulates that target's activity to provide therapeutic benefit to individuals with a disease. The ultimate validation of a target is the creation of an effective therapeutic molecule. This is a long and costly endeavour with more failures than successes. The goal of Open Targets is to transform this process by predicting if the modulation of a target is likely to provide therapeutic benefit. This would be done much earlier in the drug discovery process than is currently possible and far in advance of having a final, approved medicine.

Points covered in this workshop:

- The projects of Open Targets consortium
- An introduction to the Open Targets Platform
- Browsing the Platform
- Pointing to alternative ways to access the data

INTRODUCTION TO OPEN TARGETS

Open Targets employs large-scale human genetics and genomics data to change the way drug targets are identified and validated. We have established a set of projects to develop both the data and analytical processes that implicate targets as valid, and the core platform to provide the information to a diverse audience of users.

The core bioinformatics team develops pipelines and a database to integrate existing target data. The core also designed, created and maintains the Open Targets Platform, a public web portal to serve the integrated data and views.

Our experimental projects focus on providing insights in the identification of targets relevant to key therapeutic areas namely:

- Oncology
- Inflammatory bowel diseases (IBD)
- Respiratory disease
- Inflammation and immunity
- Neurodegenerative diseases

We also aim to develop standard epigenome profiles of cell models in use within the pharmaceutical industry and academia and establish a systematic approach for the determination of human biological and disease relevance.

More details can be found in our Projects page.

Retrieving data from Open Targets with our Platform

The Open Targets Platform is a web application that integrates and displays publicly available biological data to foster the discovery and prioritisation of targets for new therapies. We use data sources as diverse as Gene2Phenotype, IntOGen, GWAS, UniProt, ChEMBL, Expression Atlas, Cancer Census, Reactome and EuropePMC as pieces of evidence to support target-disease associations. The associations are scored using objective statistical and computational techniques.

In our release (December 2016), the Platform provides information on 31,071 targets; 8,659 diseases; 4.9 million evidence; and 2.5 million target-disease associations.

In addition to the web application, we include the data dumps, a REST API and a Python client.

The Open Targets Platform is aimed at users from both academia and industry, whether they want to browse a target on a gene by gene (or disease by disease) basis, carry out more complex queries using the API, or download all evidence and association objects for downstream analyses.

Synopsis: what can I do with the Open Targets Platform?

- Find out which targets are associated with a disease
- Explore the evidence supporting this target-disease association
- Export a table with the FDA drugs currently in clinical trials
- Discover if there other diseases associated with a given target
- Get the association of a target with diseases from different therapeutic areas
- Find target specific information, such as baseline expression, protein structure, alternatively spliced transcripts, gene trees
- Get disease target specific information, such as a classification based on the ontology of the disease and the drugs mapped to it

Help documentation and support

- Data sources in the Open Targets Platform
- View our FAQs
- Email us

Connect with us

- Open Targets Blog
- Follow us on Twitter
- Check our page on Facebook and LinkedIn

Further reading

Koscielny, G. *et al.* Nucleic Acids Res (2017 Database Issue): http://nar.oxfordjournals.org/content/early/2016/11/29/nar.gkw1055

A breakthrough article from Nucleic Acids Research: http://www.narbreakthrough.com/

OPEN TARGETS PLATFORM: LIVE DEMOS

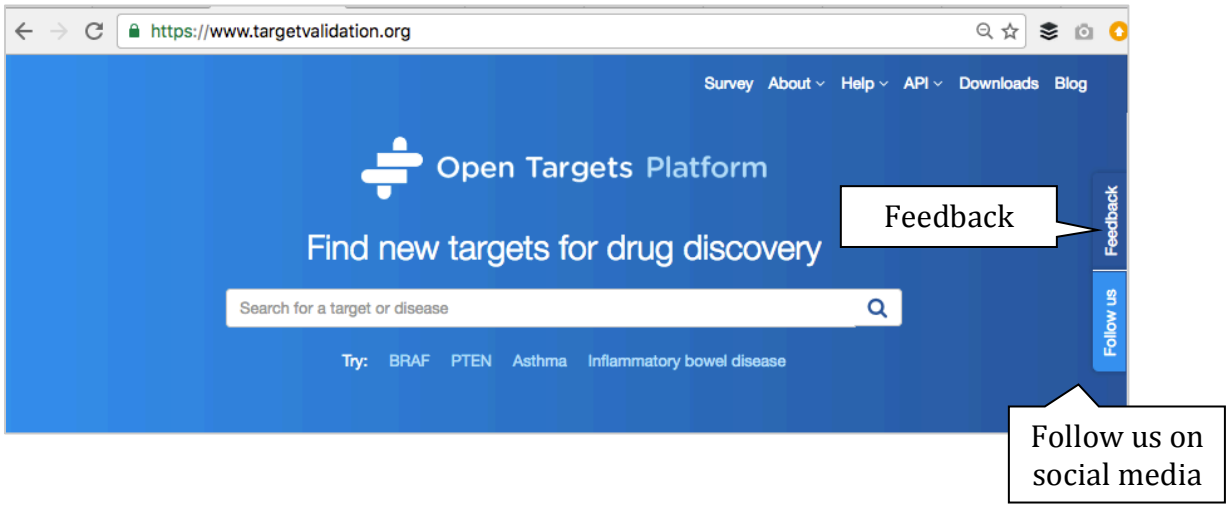
We will guide you through the website using multiple sclerosis, as an example and exploring the *CD86* gene.

The following points will be addressed during the walkthrough:

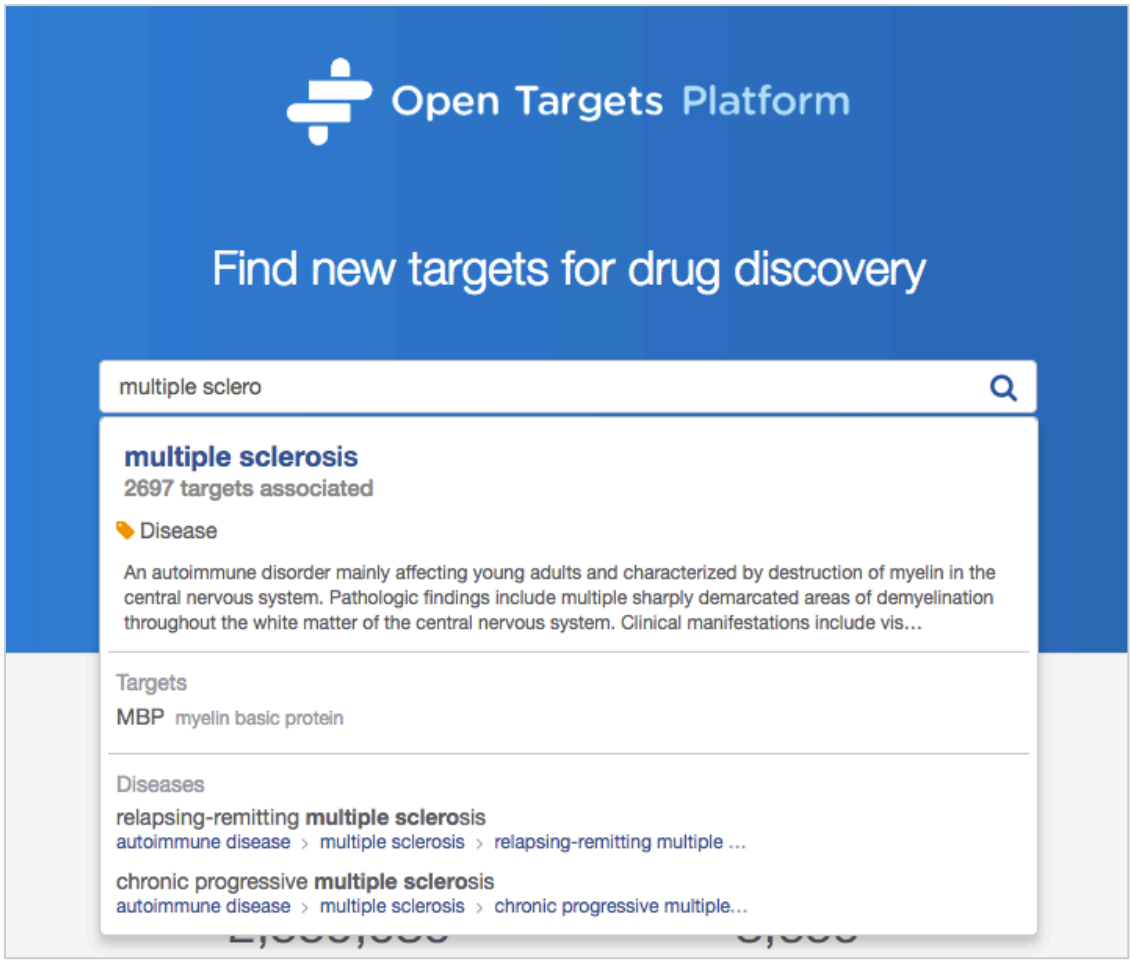
- How to find targets associated with multiple sclerosis
- How to filter down the number of targets based on specific type of evidence
- How to find the data sources used to support the target-disease association
- How to look for other diseases (than multiple sclerosis) associated with a given target
- How to visualise a target in a browser-like view
- How to find out how strong the association between a target and a disease is
- How to find drugs currently in clinical trials
- How to filter **our** associations by **your** list of target genes

Demo 1

Go to www.targetvalidation.org and search for multiple sclerosis.



Select the first (best) hit:



You will see a page like this:

The current release of the Open Targets Platform (December 2016) lists 2697 targets associated with multiple sclerosis.

The data types supporting these results are based on Genetic association, Drugs, RNA expression, Text mining, and Animal models.

Check our help page to find out more about our data sources: https://targetvalidation.org/data_sources.

You can filter the number of associations by 'Data types', 'Pathway types', 'Target class' and by uploading 'Your target list':

A) Data types

- Genetic associations (e.g. GWAS catalog)
- Somatic mutations (e.g. Cancer Gene Census, EVA)
- Drugs (from ChEMBL)
- Affected Pathways (from Reactome)
- RNA expression (from Expression Atlas)
- Text mining (from EuropePMC)
- Animal models (from PhenoDigm)

B) Pathway types
    Signal Transduction
    Metabolism
    …
C) Target class
    Enzyme
    Membrane receptor
    …
D) Your target list
    Upload your own list of genes (in official gene symbols from HGNC or Ensembl Gene IDs)

What are **Data types, Pathway types** and **Target class**?

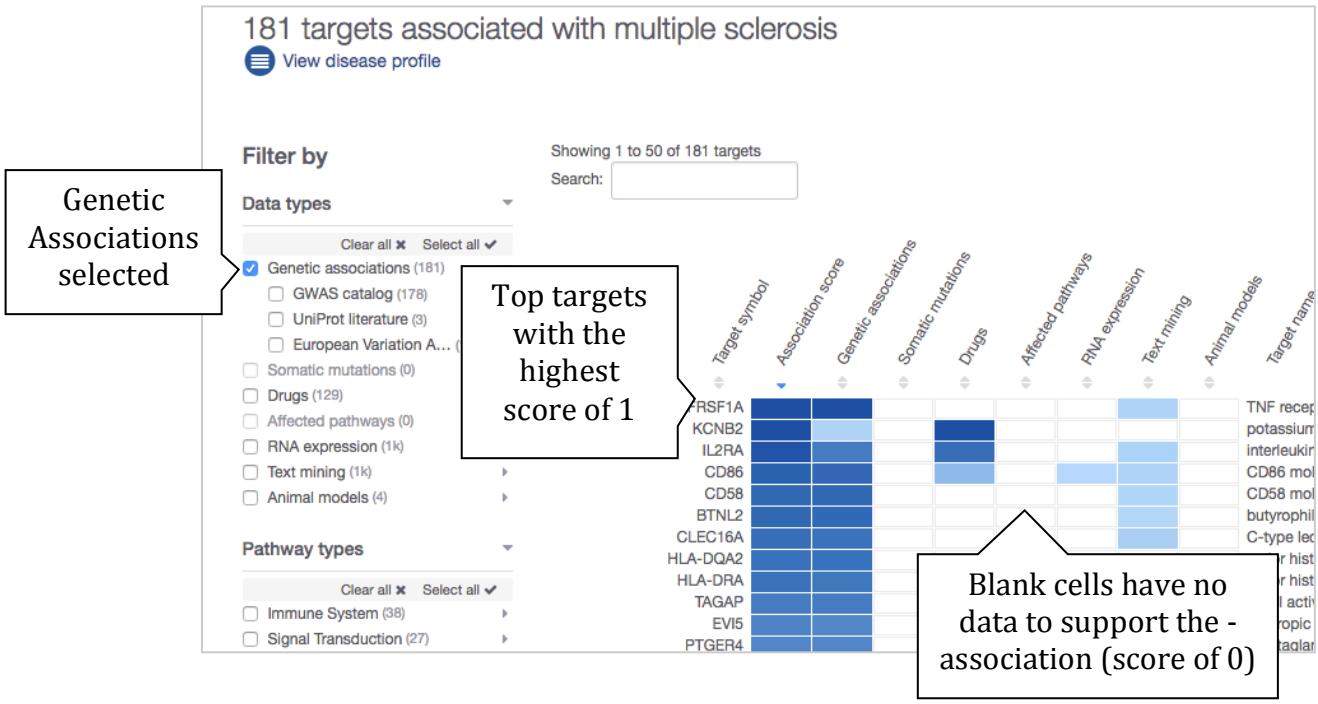
We collect data from various sources and combine them into categories called Data types. Example of data sources are GWAS catalog and UniProt, both combined into Data types. Note that data from an individual source can contribute to different Data types, e.g. data from EVA is observed in two data types, Genetic associations and Somatic mutations.

'Pathway types' are defined by Reactome:

(http://www.reactome.org/),

whereas the categories within 'Target class' are defined by ChEMBL (https://www.ebi.ac.uk/chembl/).

Let's now filter the data to focus on 'Genetic associations' (Data type) only. The number of targets goes down to 181:



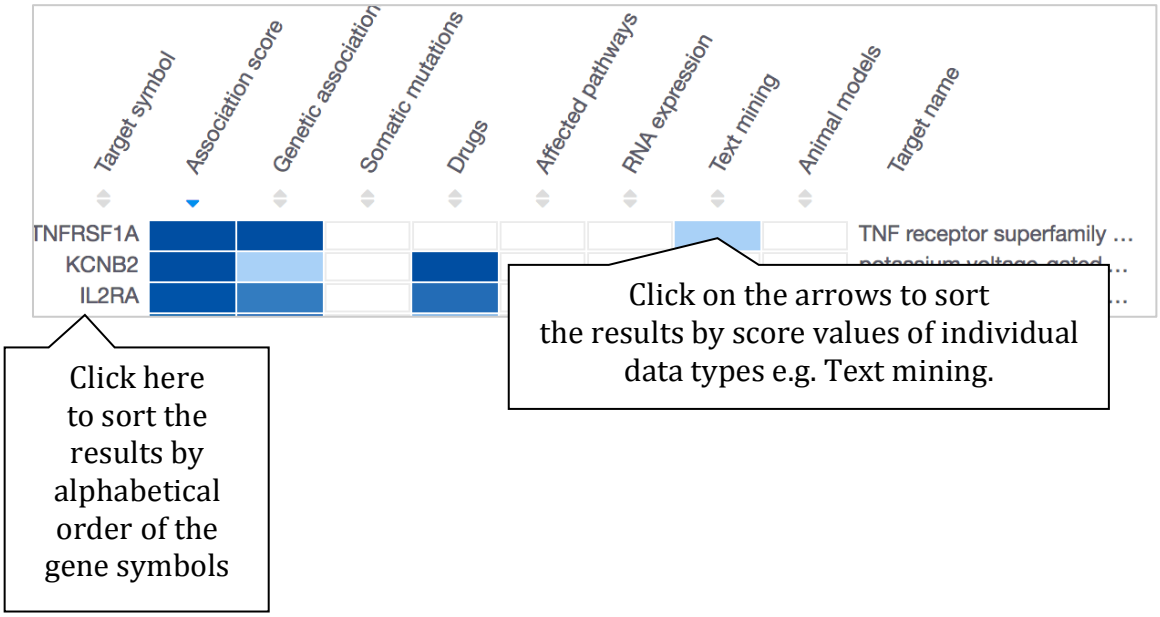
These are targets associated with multiple sclerosis based on genetic variants only. Genetic variants are SNPs (single nucleotide polymorphisms or mutations, or short indels) from the GWAS catalog, UniProt and EVA (European Variation Archive) sources only.

The table is sorted by default with the best hit on the top of the table i.e. *TNFRSF1A*. The best hit is the target that contains the highest (overall) association score. Different weight is given to different data types when computing the score:

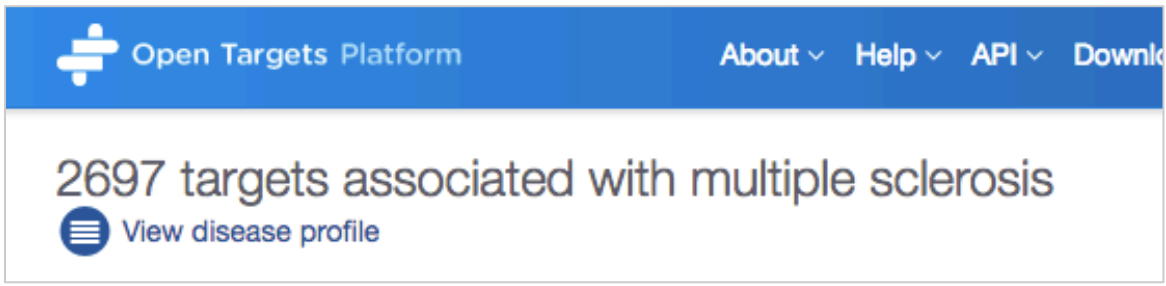
From highest to lowest weight of all data types:

Genetic association = somatic mutations = drugs = pathways
RNA expression
Animal models = Text mining

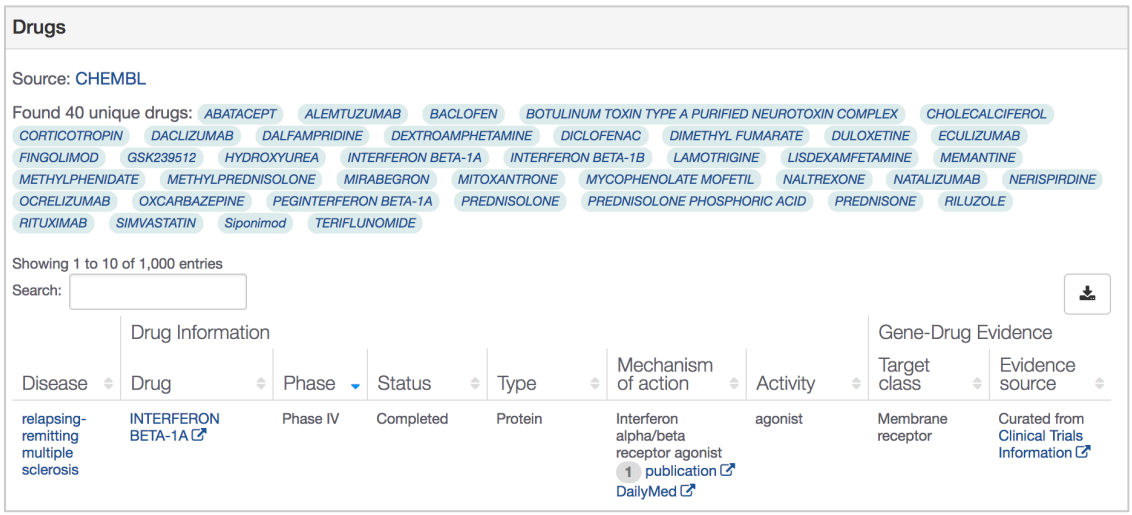
You can sort the table by alphabetical order of the list of targets, or by the association score (either overall or per data type e.g. Genetic associations, Drugs, Text mining, etc). The association score varies from 0 to 1, the closer to 1 the stronger the association. This score is computed for each piece of evidence that is used to support the association. Individual scores within data sources and data types are combined to give the overall score ('Association score' column in the table below):



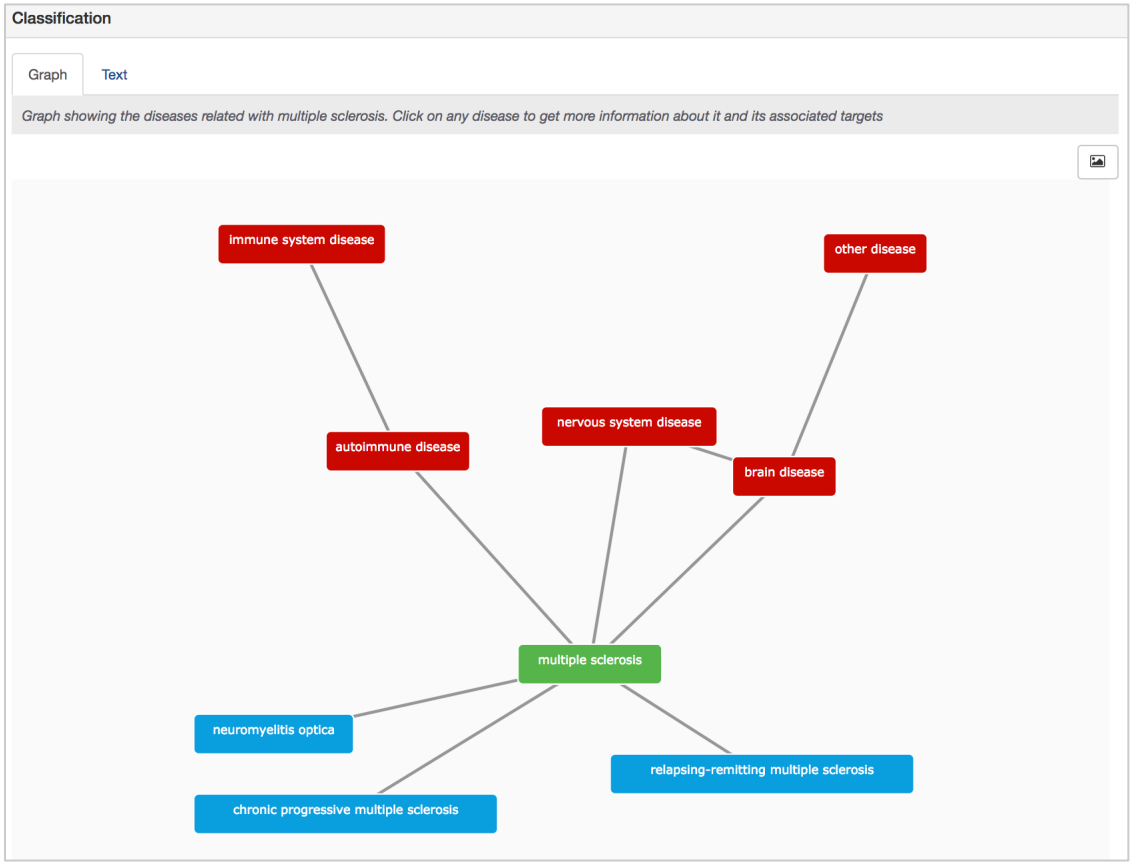
To see which drugs are used in the clinical trials with patients with multiple sclerosis (or children terms of this disease), click on the 'View disease profile':



Let's now expand the tab 'Drugs' to get a list of all drugs (n = 40 unique drugs in the December release) in different phases of clinical trials. You can filter (and sort) the table by disease, phase of clinical trial (e.g. IV, the most advanced phase), class of the target (e.g. membrane receptor), etc. You can also download this table in csv (comma separated value):

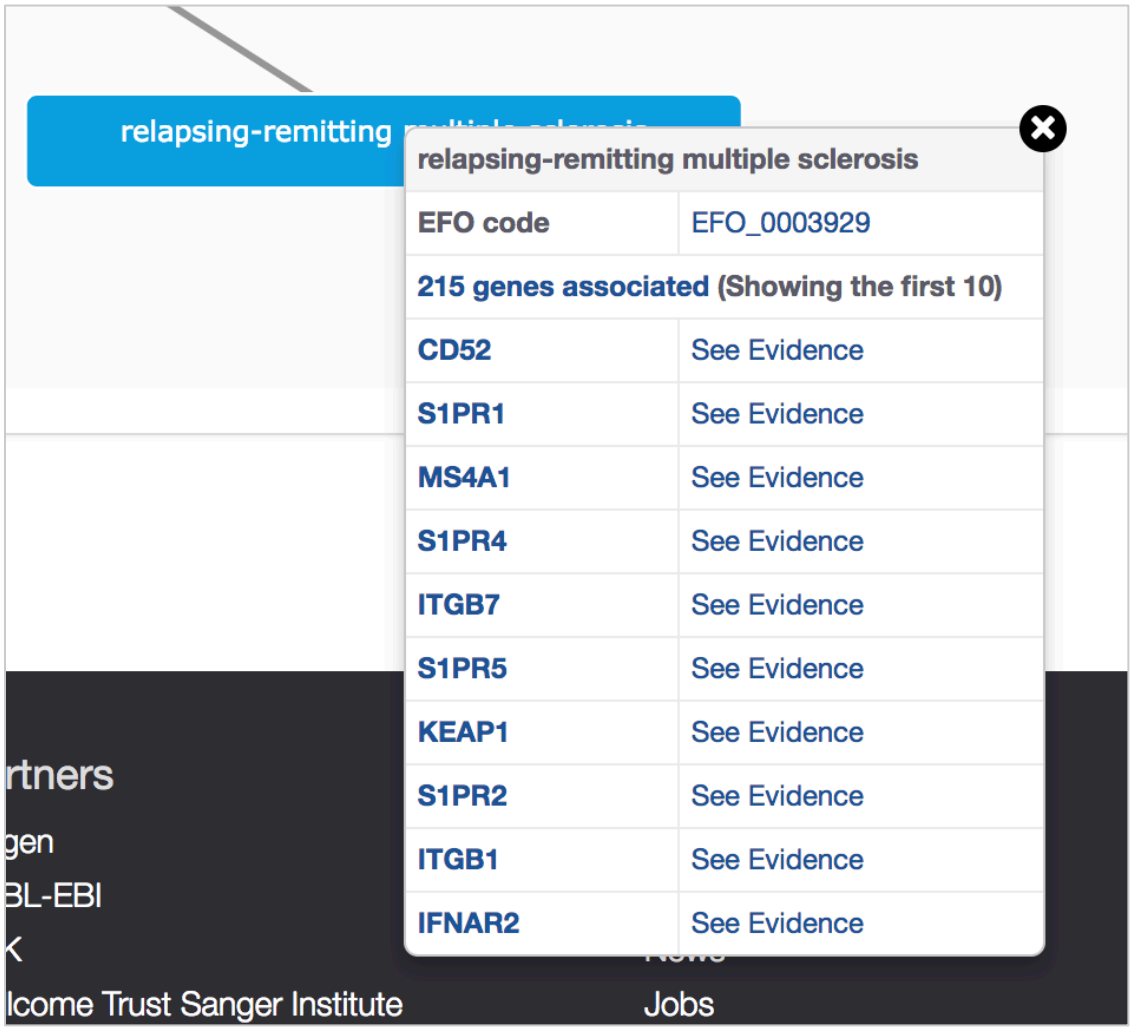


Scroll down to view the disease ontology (disease relationship) in the 'Classification' tab. The data on the relationship of diseases comes from the EFO (Experimental Factor Ontology).



Multiple sclerosis is the disease of interest in this tutorial, and is represented in green. Red nodes correspond to parental terms in relation to multiple sclerosis, whereas its children terms (e.g. chromic

progressive multiple sclerosis) are shown in blue. Click on any of disease names to get the targets associated with them:

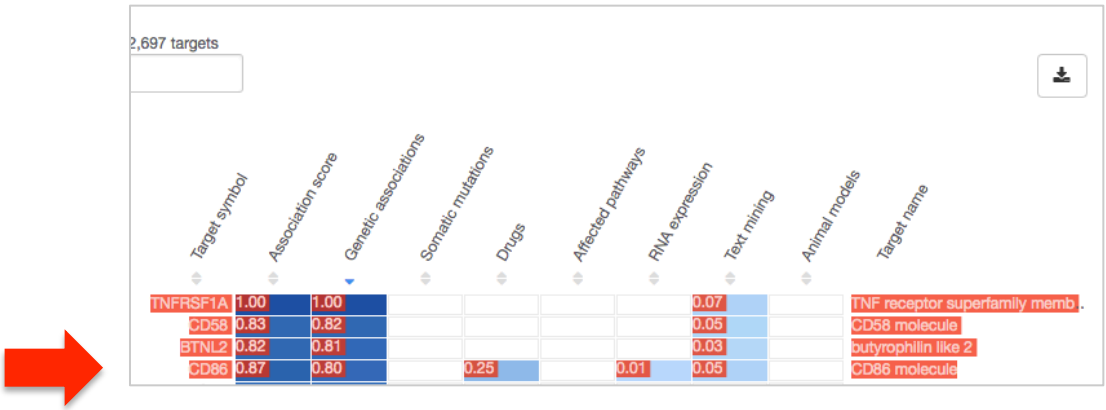


By using the EFO parent-child (subclass of) relationships, we derive new associations that may not have direct evidence. For instance, IBD is an autoimmune disease and the direct evidence of targets associated to IBD are propagated to the higher autoimmune level to allow users to find common targets across groups of related diseases (e.g. Ulcerative Colitis, Crohn's disease and IBD). In EFO, 'asthma' is a 'respiratory system disease' and 'childhood onset asthma' is a subclass of 'asthma'. Both evidence from 'asthma' and 'childhood onset asthma' are propagated to 'respiratory system disease'

Demo 2

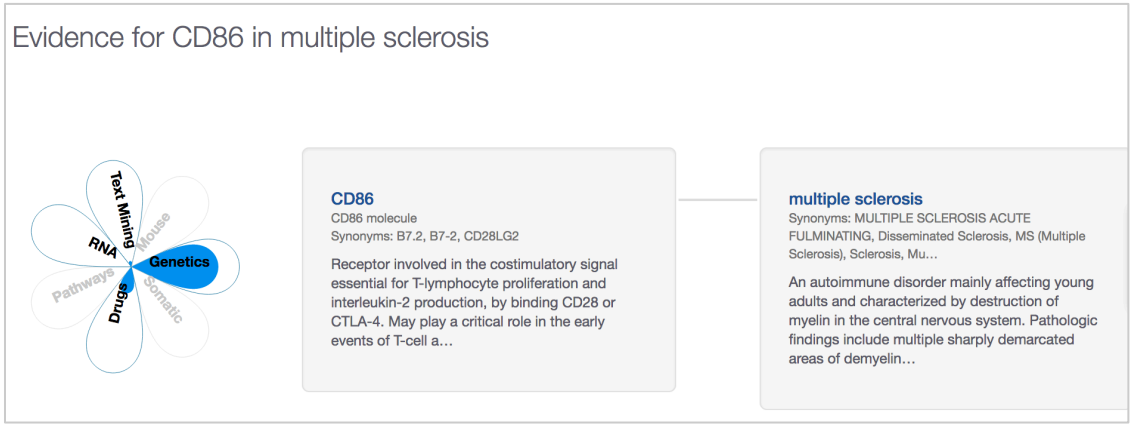
Let's now explore the evidence used to associate *CD86* and multiple sclerosis. We've chosen this target for follow up based on the availability of information for different data types.

Click on any row corresponding to CD86 in the table below:



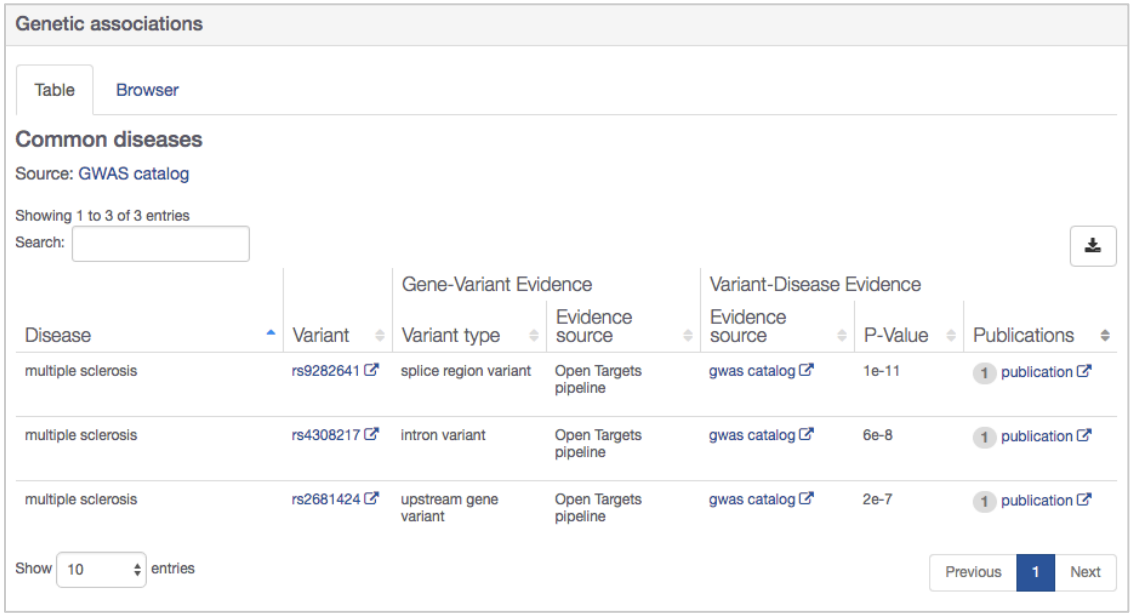
The data types that support this association are (check the flower and the coloured petals):

Genetic association
Drugs
RNA expression
Text mining



Note: If you wish to suggest data types or resources we could/should incorporate into our Platform, please get in touch: support@targetvalidation.org

The genetic evidence that supports the association (*CD86* – multiple sclerosis) comes from the Gwas catalog. They are all known in public databases i.e. dbSNP (hint: the rsID such as rs9282641, rs4308217 and rs2681424.

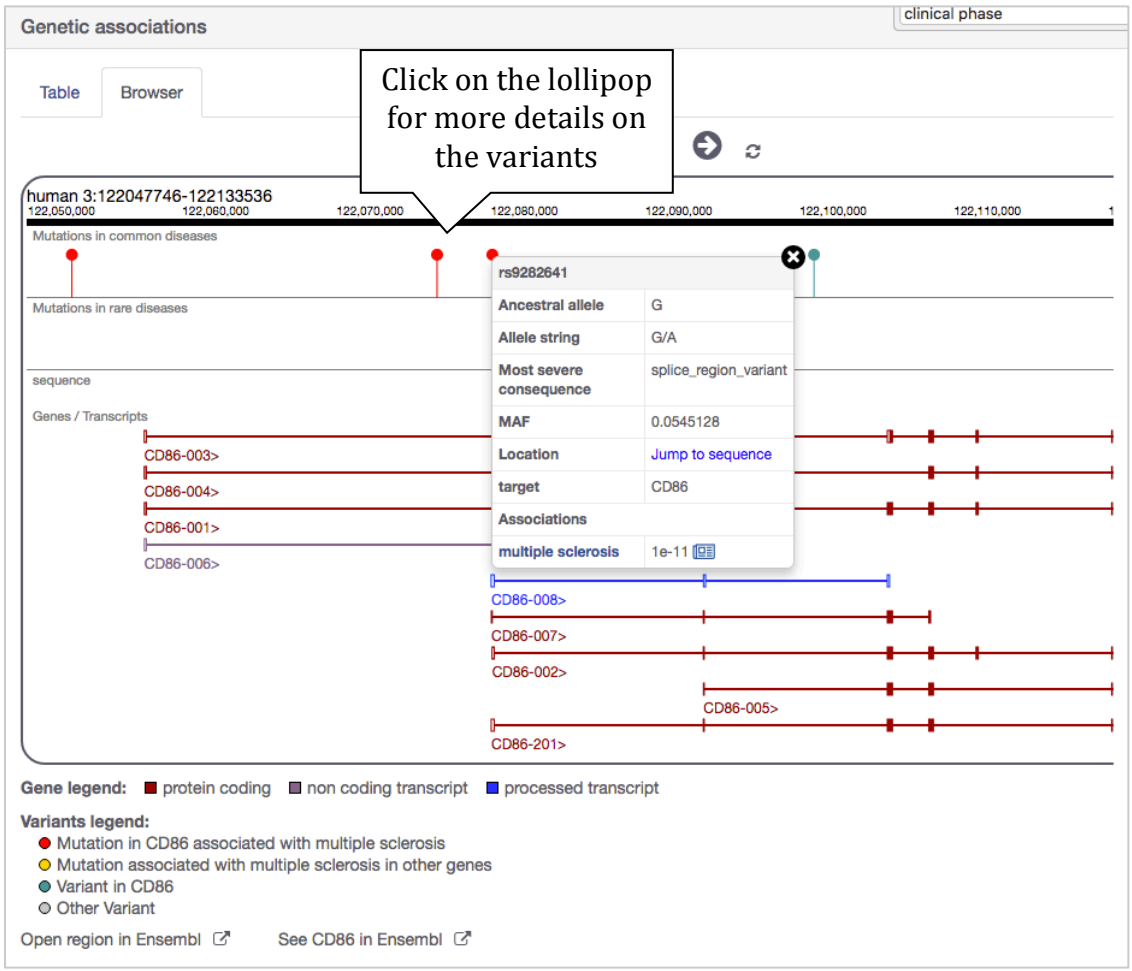


In addition to the table above, you can also explore the 'Genetic associations' data in a Browser view.

In the Browser view, you can zoom in and out, scroll along the genome and find out more about the gene (s), transcript (s), and the genetic variants (represented as lollipops) in the genomic region depicted.

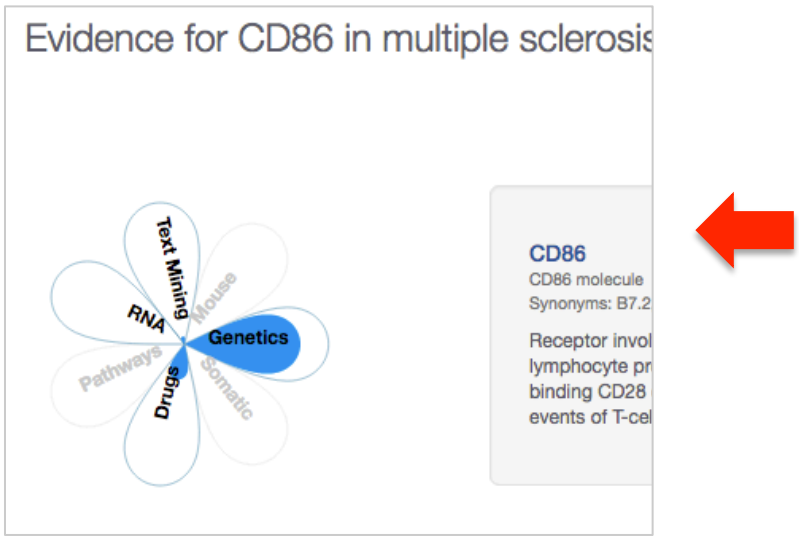
Note: The assembly we use is human assembly GRCh38, also known as hg38.

We also provide links to Ensembl.

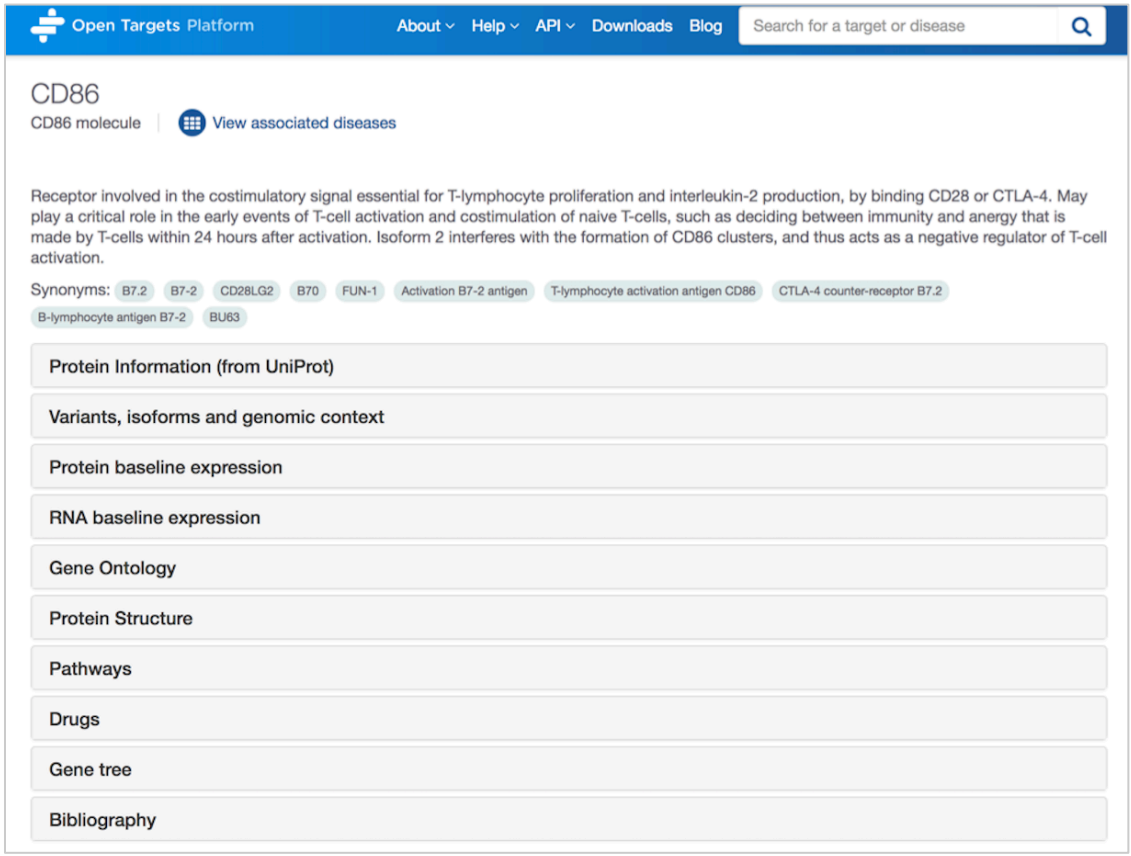


To find out if there are drugs currently in clinical trials targeting *CD86* in patients with multiple sclerosis, let's expand the 'Drugs' tab. There is just one drug (i.e. ABATACEPT) on phase II of clinical trials.

We can now scroll back to the top of the page and click on the 'CD86 link (next to the flower) to explore this target in more details, such as to find out its RNA expression levels across several tissues and whether or not it is associated with other diseases of the nervous system.



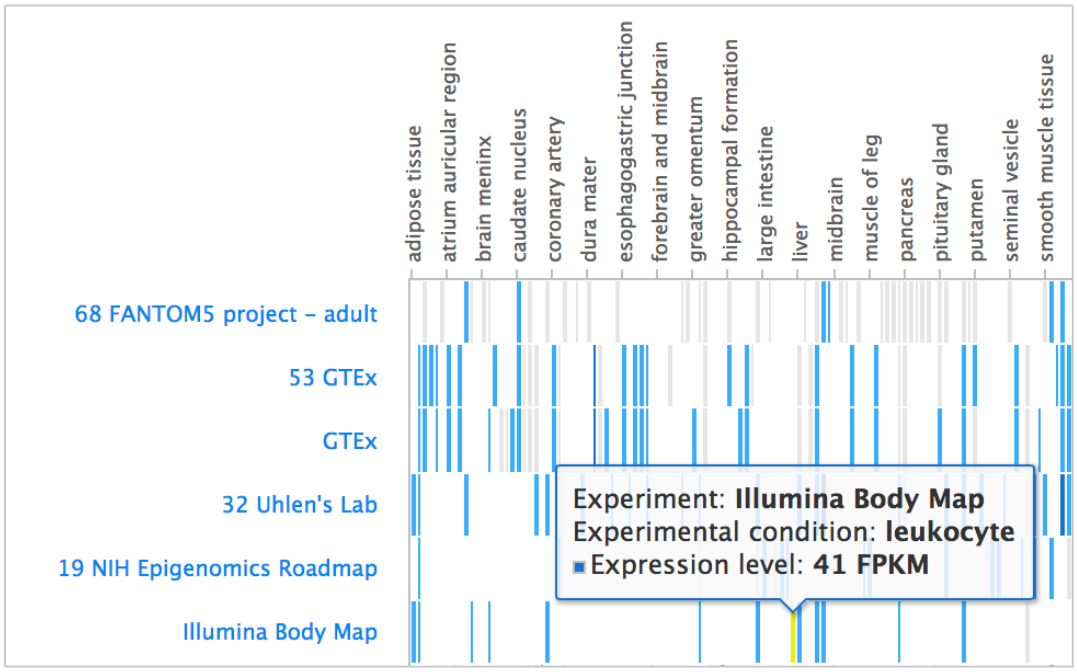
You will land on a page like this:



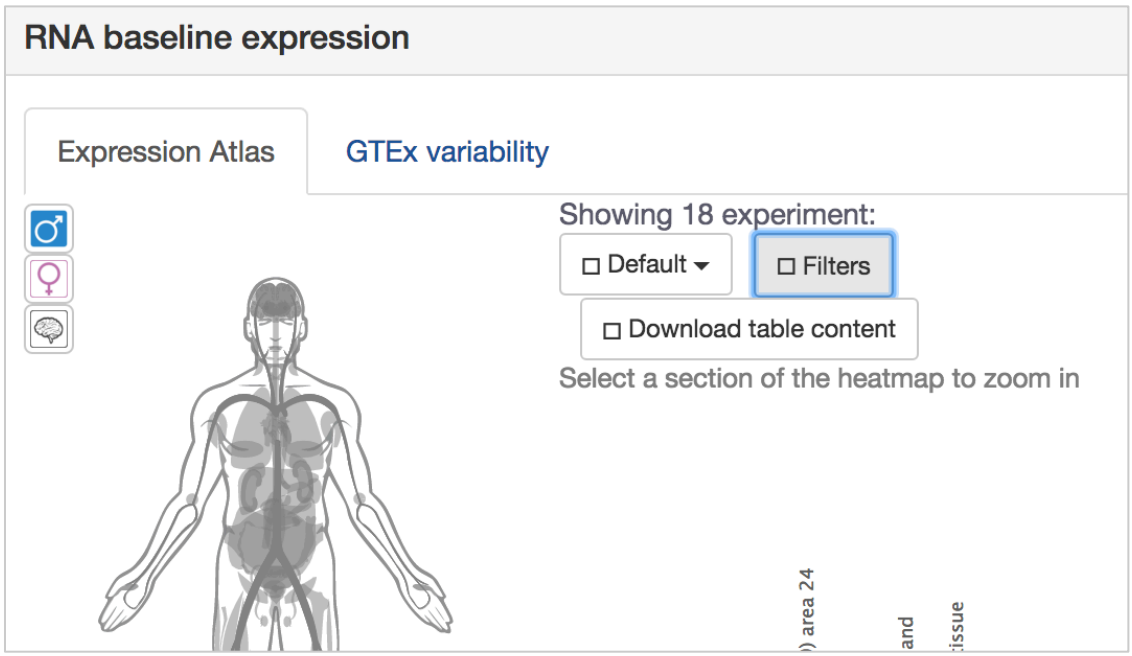
Expand the 'RNA baseline expression' to find out in which tissues *CD86* is highly expressed.

You will find two tabs in there: one with Expression Atlas data (with data from several projects including the Illumina Body Map), and one with GTEx data only:

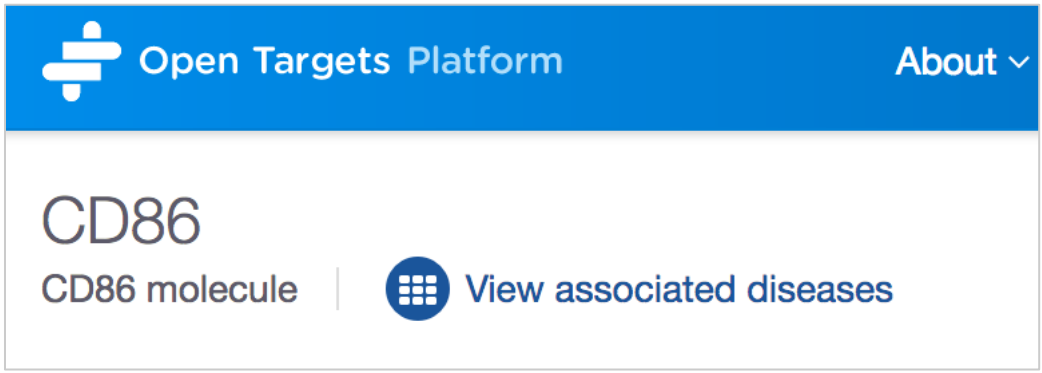
According to the Illumina Body Map data, leukocytes are the cells with the highest expression level for the *CD86* gene:



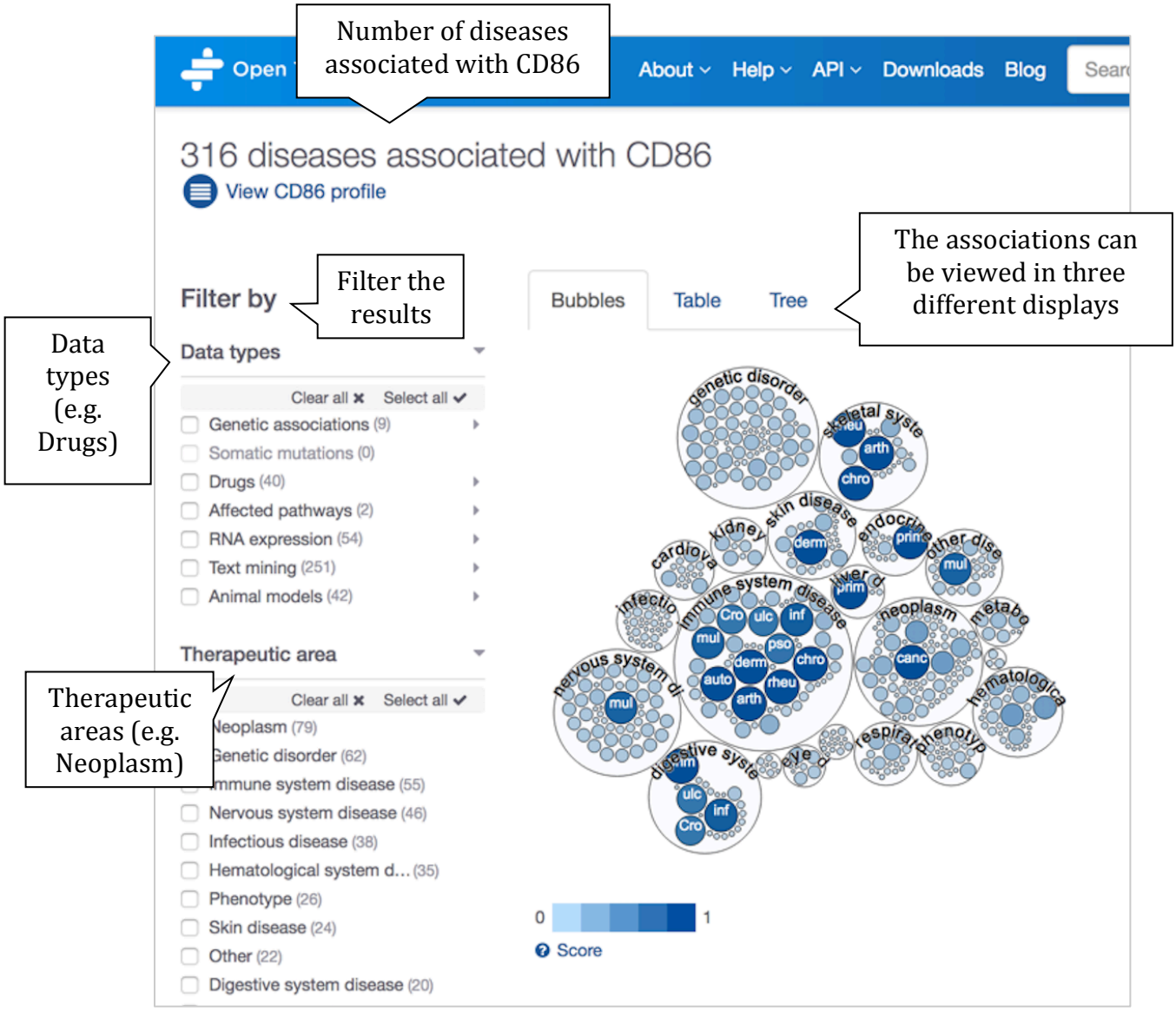
You can zoom this view in and out and apply filters such as 'Expression Value' (below cutoff, low, medium or high) and Anatomical Systems.



Let's now click on 'View associated diseases' to find out all diseases associated with the *CD86* (not only multiple sclerosis)*:*



You will land on a page like this:



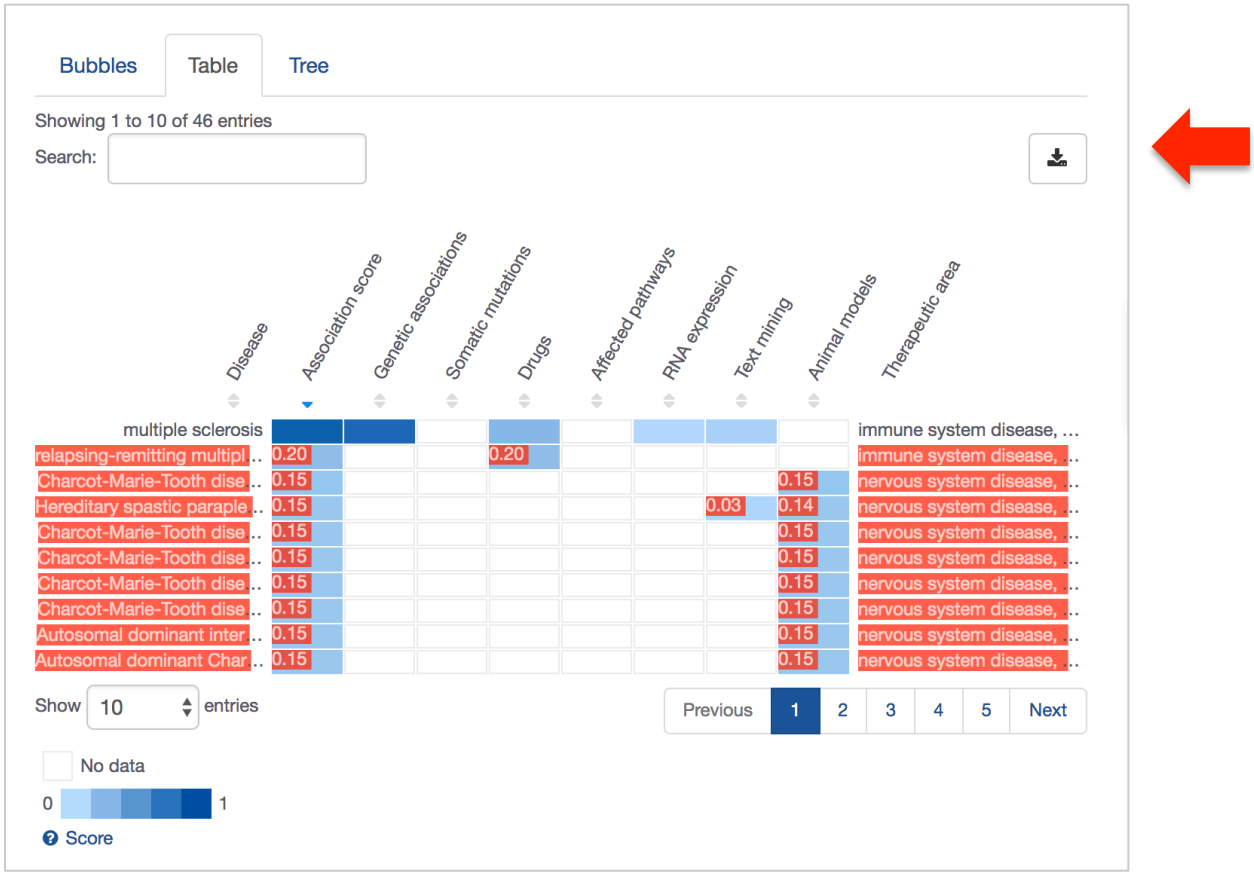
There are three different displays that can be used to view the diseases associated with any given target:

- Bubble view

In this view, we group diseases into 'bubbles' based on the disease ontology. Large bubbles correspond to a therapeutic area and consist of smaller bubbles representing diseases within this area. A disease can belong to several therapeutic areas and therefore can appear within more than one large bubble. The strength of the association between the target and a disease is represented by the size of the bubble and the shade of its blue colour; the larger the bubble and the darker the blue, the stronger the association.

- Table view

In this view, we list all diseases associated with a target, ordered by the association score, which is colour coded. When there is no evidence to support the association, the cells in this table are coloured in white (score of zero). You can show the 10 first entries and get the pagination for the remaining entries.

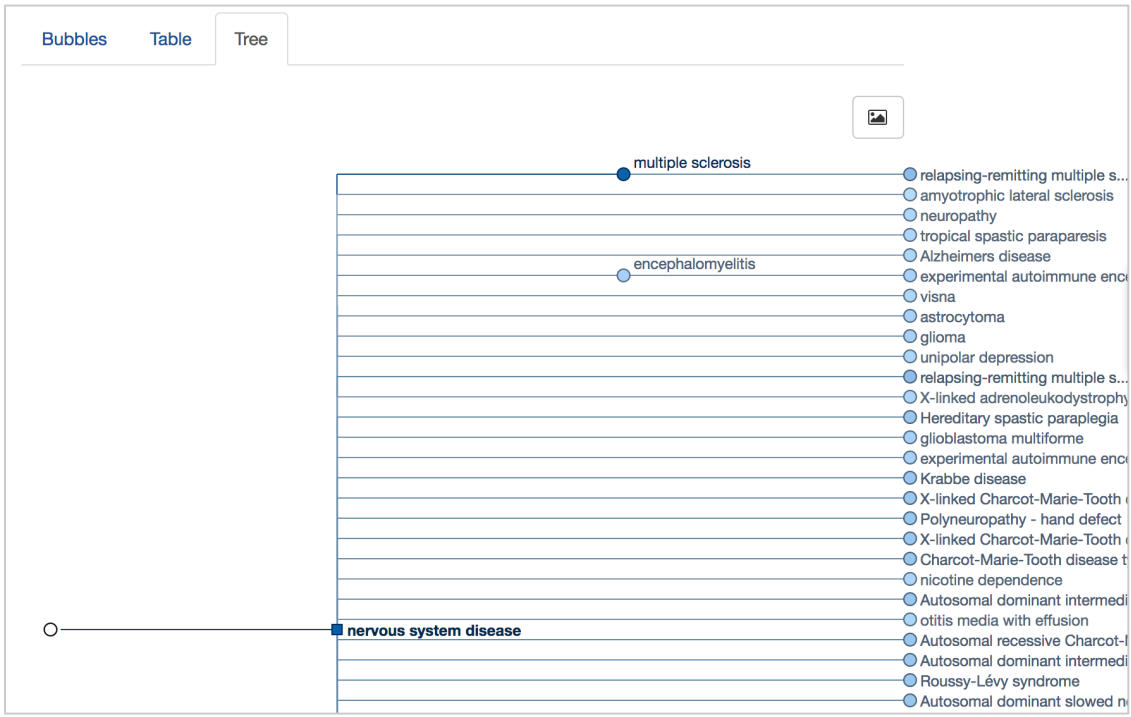


This table can be exported in csv format (look for the download button).

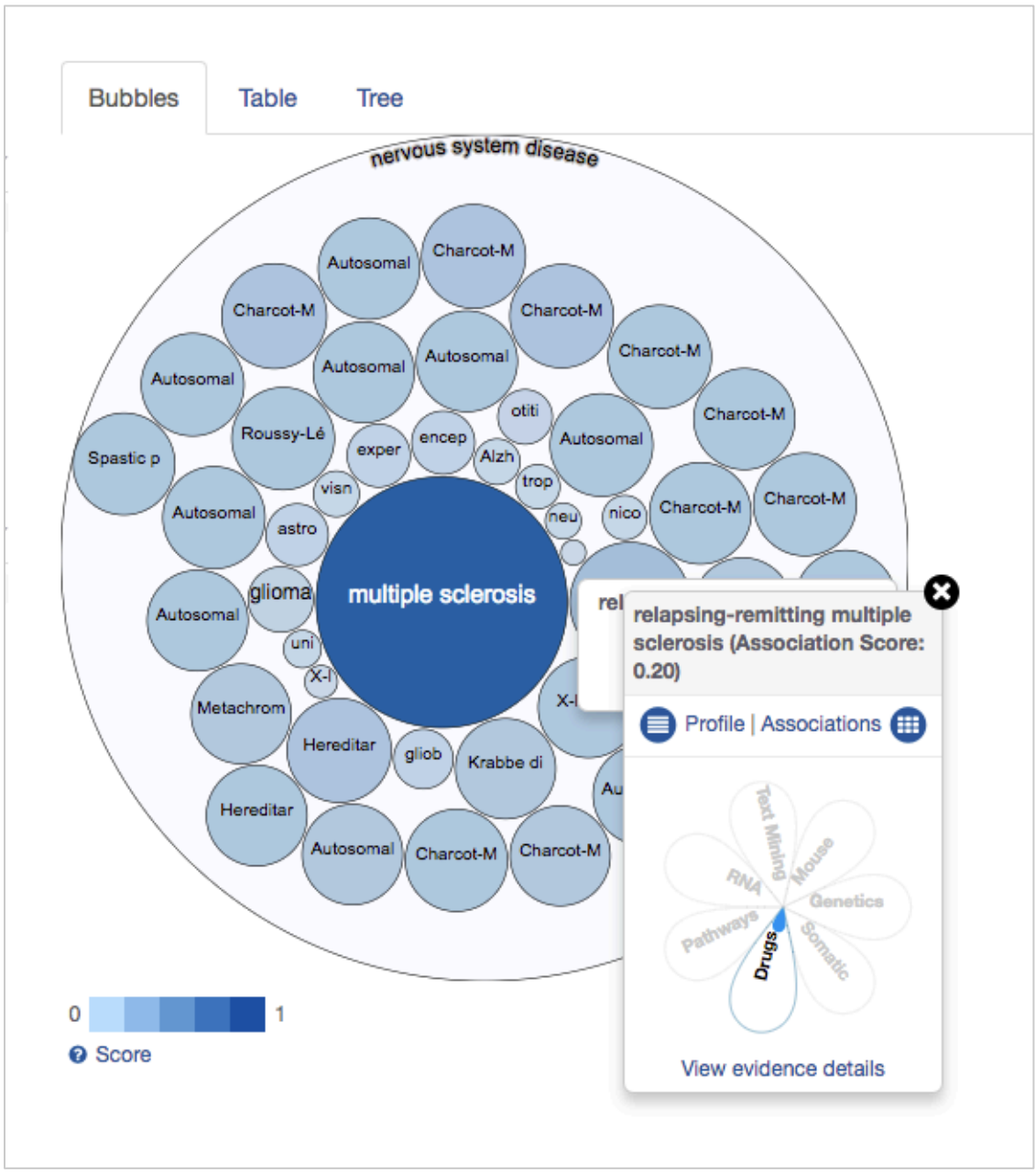
Tip: We colour code the cells in the table in different shade of blue as a visual way to convey the strength of the association (strongest association is coloured in dark blue). The score varies from 0 to 1. Hover over the cells in the table to view the numbers. Alternatively, you can select the cells in the table so that you can view the numerical values.

- Tree view

In the Tree view, you can visualise the evidence across the therapeutic areas in a tree format that represents the relationships of diseases. Therapeutic areas have a square symbol (e.g. Genetic disorders), while the diseases (e.g. ovarian carcinoma) are represented as circles. The squares and circles are colour coded in blue, and the darker the blue, the stronger the association:



Regardless the view you choose to explore, you can filter the data to find out if there are other “Nervous system” diseases associated with this target. There are 46 of them (e.g. Hereditary spastic paraplegia, amyotrophic lateral sclerosis and neuropathy). The scores vary from 0.01 to 0.20.


Bubbles
Table
Tree
nervous system disease
multiple sclerosis
glioma
Autosomal
Charcot-M
Roussy-Lé
Spastic p
exper
encep
Alzh
otiti
trop
neu
nico
visn
astro
uni
X-l
Metachrom
Hereditar
gliob
Krabbe di
0
1
Score
relapsing-remitting multiple sclerosis (Association Score: 0.20)
Profile | Associations
Text Mining
Mouse
RNA
Genetics
Pathways
Drugs
Somatic
View evidence details

HANDS-ON EXERCISES

Exercise 1

Aducanumab, antibody that may slow the progress of Alzheimer's disease

BACKGROUND
The most common cause of dementia, Alzheimer's disease is a brain disorder that leads to impairment of intellectual functions and social skills, resulting in significant disturbance of daily living activities. Dementia is caused by the destruction of cells in certain parts of the brain primarily involved in memory and mental function.

SIGNIFICANCE
Alzheimer's disease is the 6th leading cause of death in the United States and it's expected 16 million Americans will be living with Alzheimer's by 2050. (source: alz.org).

Biogen in collaboration with Neurimmune has been conducting clinical studies investigating a potential new treatment (Aducanumab) for early Alzheimer's disease. Aducanumab is an antibody that binds to and may reduce amyloid plaques from the brain, potentially slowing the progress of the disease.

QUESTIONS
a) Can you use the platform to find out if this drug is currently used in trials with other dementia related diseases?

b) Which genes does this drug match to?

c) Can you list the diseases from the nervous system where there is a strong confidence (>90%) in the association with this gene?

Let's focus now on the different evidence used to associate *APP* with Alzheimer's.

d) Are there any known genetic variants (i.e. with a reference ID such as rs123456) listed in the Genetic associations table? Can you find some of the papers that support this association?

e) Click on the 'Browser' link to view the mutations is a graphical display. Are there variants associated with other traits (or diseases) in the region of the *APP* gene?

f) Which biochemical pathways seem to be affected by pathogenic mutations in this target?

Let's now have a look at the target itself by clicking on the target name. This page provides a profile for a target and it's where you can explore more information on a target such as data on RNA baseline expression, gene tree with orthologous genes in other species, etc.

g) Which tissues according to the GTEx project does this target seem to be highly expressed?

Exercise 2

***MS4A1* as a possible drug target in the treatment of non-Hodgkin's lymphoma**

BACKGROUND
The B-lymphocyte antigen CD20 is an activated-glycosylated phosphoprotein expressed on the surface of all B-cells beginning at the pro-B phase and progressively increasing in concentration until maturity. In humans, the MS4A1 gene encodes antigen CD20.

SIGNIFICANCE
CD20 is the target of monoclonal antibodies (mAb) in the treatment of all B cell lymphomas, leukemias and autoimmune diseases. Some of these active agents (mAb) are on clinical trials for non-Hodgkin's lymphoma. Others anti-CD20 mAB have been approved by the FDA for B-cell chronic lymphocytic leukemia.

QUESTIONS

a) How many diseases within the broader Therapeutic area 'Hematological system' are associated with this target? How many of these are based on 'Drugs' only?

b) In addition to the data evidence 'Drugs', are there other types of evidence supporting the association between *MS4A1* and non-Hodgkin's lymphoma?

c) Let's now explore some disease information available for non-Hodgkin's lymphoma. Can you list all drugs in phase IV of clinical trials for the treatment of this disease which status is completed (i.e. no longer recruiting patients for the clinical trials)?

d) Can you find the different subtypes i.e. the children terms of non-Hodgkin's lymphoma in its ontology? Can you download this image?

Note: you may want to click on the children diseases and see which targets have been associated with them.

Exercise 3

***RS1*, a gene playing a role in the retina layer formation**

BACKGROUND

QUESTIONS

a) What are the eye diseases that seem to be associated with this target based on a combination of genetic evidence (e.g. SNPs from GWAS), text mining of the literature and mouse models?

b) How long is the protein encoded by this gene/target?

c) Which chromosome does this gene map to on the human genome? Is it a forward or reverse stranded gene?

d) Which tissue has the highest RNA baseline expression from the FANTOM5 project?

Demo 3

Filter the target association table for Alzheimer's based on a list of known targets.

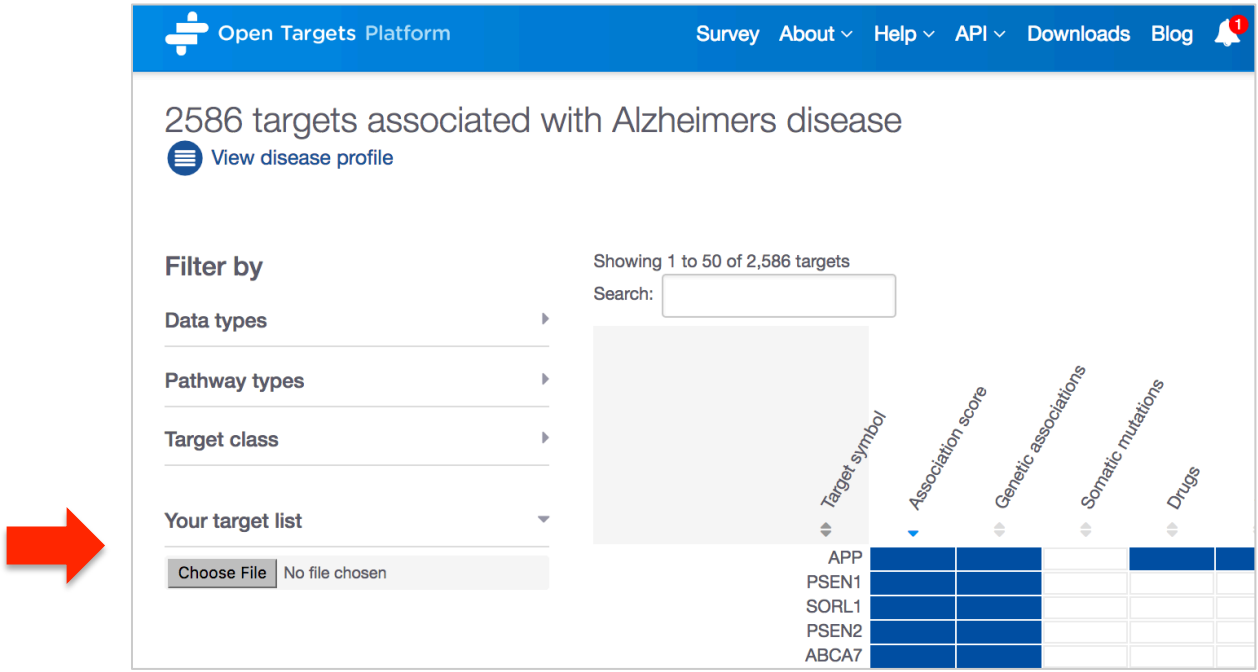
This is a list of several genes that seem to be associated with Alzheimer's based literature searches:

HFE
PSEN1
TF
APOE
ADRB2
PSEN2
A2M

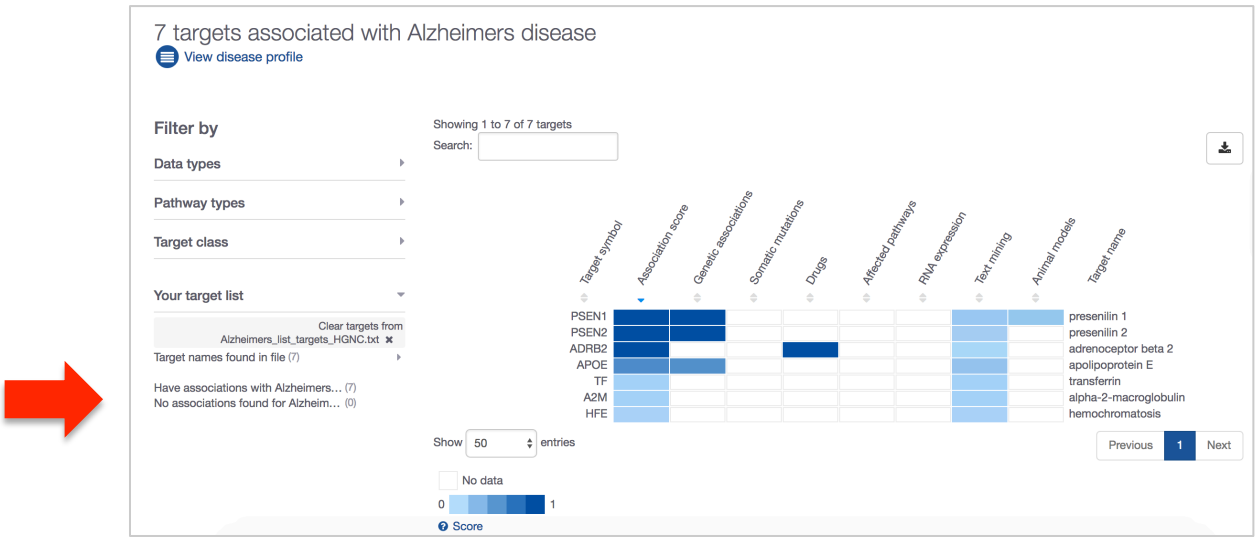
Which information is available in the Open Targets Platform that could help you to choose and prioritise a target out of that list for follow up? We can input this data as a list (in .txt) to filter the associations for Alzheimer's in Open Targets.

a) Which of those seven genes have the strongest association w/ Alzheimer's?

Firstly, let's search for Alzheimer's and then upload our target list onto the Platform:

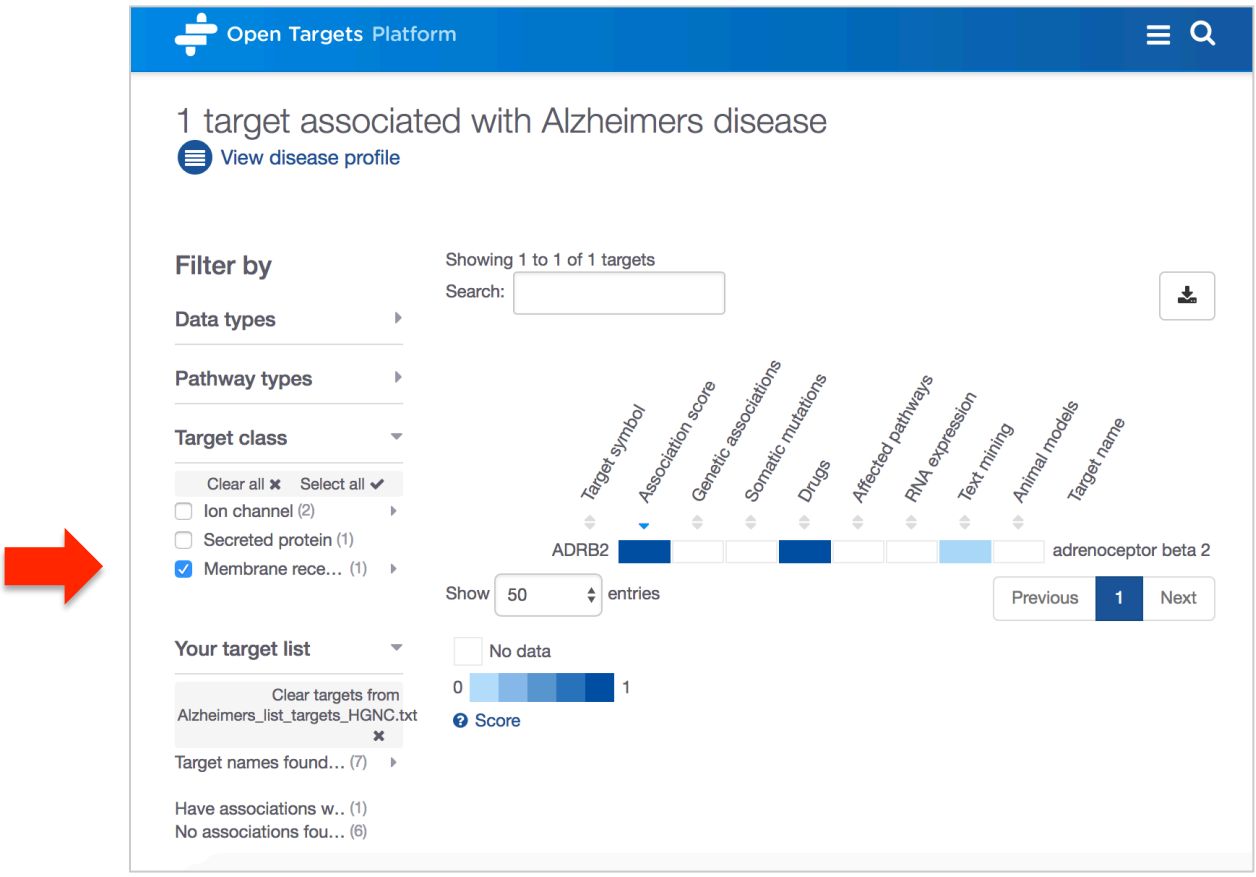


Now, we can upload a text file containing our list of genes (either as official gene symbols from HGNC e.g. *SOX3*, or Ensembl gene IDs e.g. ENSG00000134595). The filter 'Your target list' is at the left hand side of the association page (you will need to scroll down to see it):



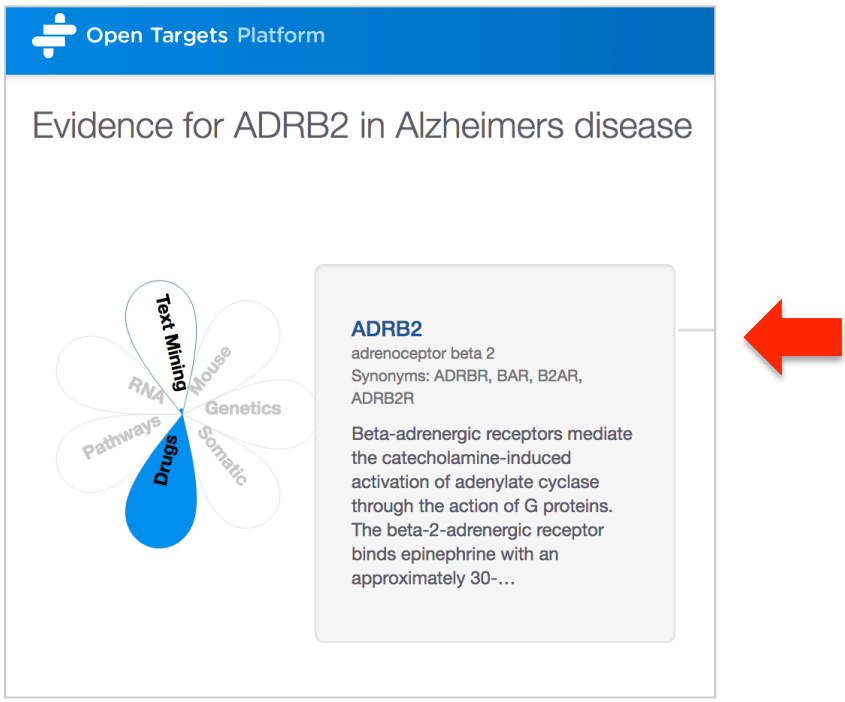
The list should be uploaded and the resulting table will show the results of our analyses for your list of seven genes (i.e. targets). This will help you prioritise which targets to follow up.

b) Are there any targets, which are membrane receptors?
We can now use the filter 'Target class' to focus on membrane receptors only. There is only one target that is a membrane receptor, *ADRB2*.

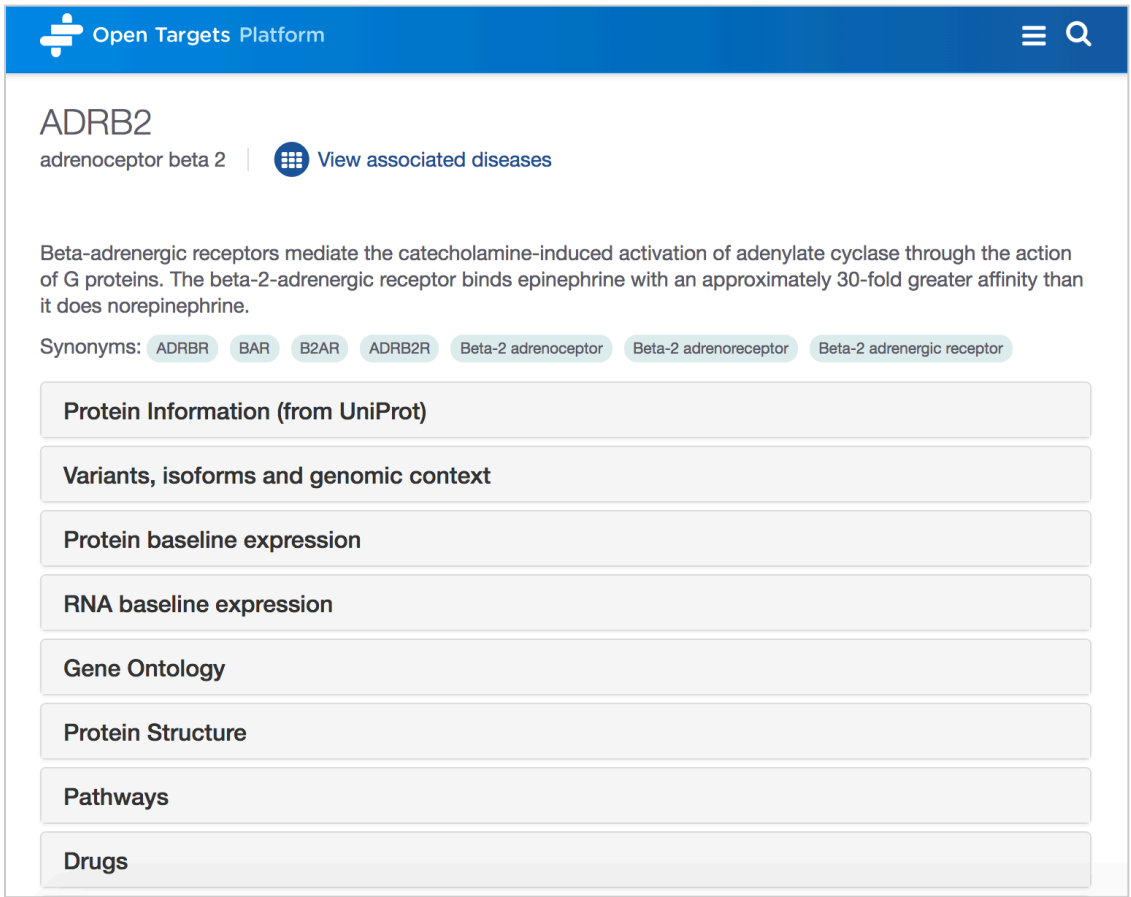


c) Which amino acids of this membrane receptor correspond to the extracellular domain?

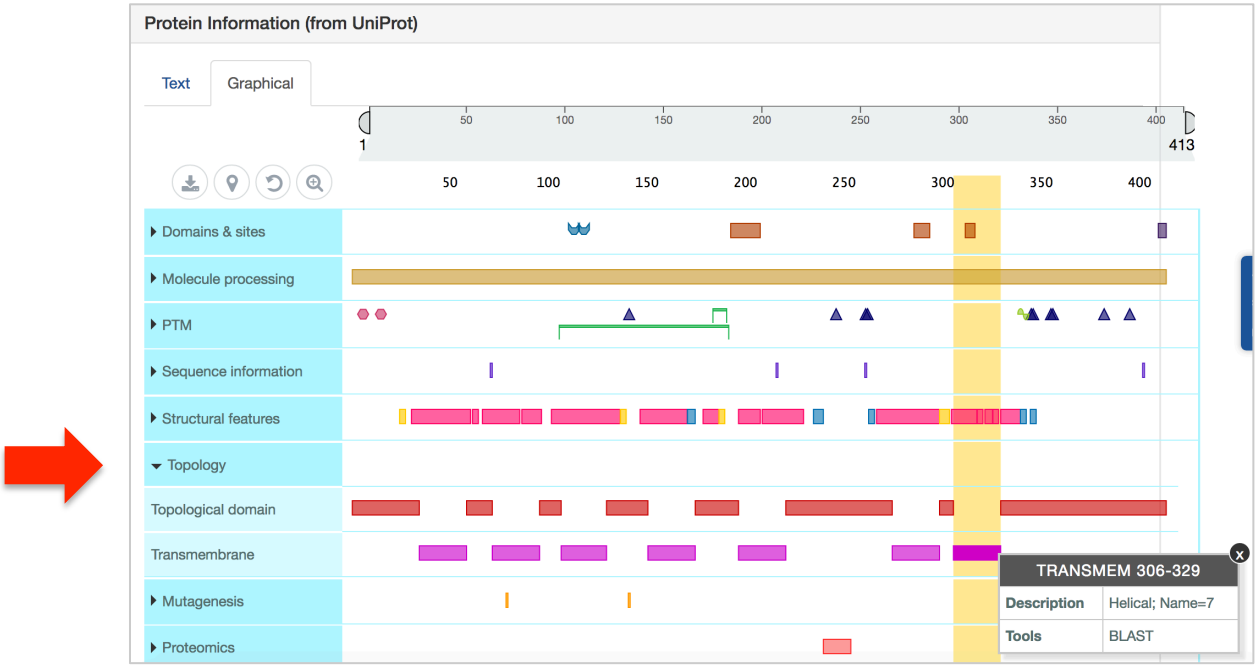
To explore more about the target itself, we can click on any cell of the resulting table then click on the target name, next to the flower:



We will land on a page like this:



To find what which amino acids of this membrane receptor correspond to the extracellular domain, we need to expand the tab 'Protein Information (from UniProt)', click on 'Graphical', then expand the 'Topology' section in the image:



This membrane receptor is a G-coupled transmembrane receptor, hence there are seven transmembrane domains. Click on the 'purple-ish' boxes in 'Topology' to get a pop up window with more information on which amino acids of the protein span the entirety of the cellular membrane.

EXTRA HANDS-ON EXERCISES

If you have finished exercises 1, 2 and 3 above, you may want to try these too:

Exercise 4

Using the Open Targets Platform to find out if the modulation of a target by a drug poses any possible unsafe interactions or effects.

BACKGROUND
The main goals of drug development are effectiveness and safety. Although no drug is 100% safe (they all have side effects), the benefits of the drugs should outweigh the known risks.

SIGNIFICANCE
Many drugs used on the treatments of diseases can interfere with other physiological processes and even cause death when taken in excess. One of the ways to start assessing the safety of a new compound is to look at which target it modulates, whether or not this target is involved in other therapeutic areas such as cardiovascular and reproductive system, and the expression of the gene (or protein) in normal tissues.

USE CASE
Abemaciclib has been shown in vitro to be a selective ATP-competitive inhibitor of CDK6 kinase activity. CDK6 has been shown to phosphorylate and thus regulate the activity of tumor suppressor protein Rb. Expression of this gene is increased in some types of cancer.

Abemaciclib is under investigation in patients with breast carcinoma among other types of cancer.

QUESTIONS
a) Which data supports the association between CDK6 and breast carcinoma?

b) Are there other drugs in addition to abemaciclib used in clinical trials modulating the same target for breast carcinoma? Can you get to the original data?

c) Are there studies showing a decreased level of RNA expression of this gene in breast carcinoma?

d) Is this target associated with cardiovascular diseases with a strong confidence (i.e. score of 0.80 or above)?

Exercise 5

How can I retrieve all disease associations for three genes of interest, all at once?

BACKGROUND
So far you have used the website www.targetvalidation.org to search for target-disease associations on a gene by gene (or disease by disease) basis. You may want to access and retrieve data on several genes or several diseases. For this, you can access our data in programmatic way using our REST API (or Python, R clients)

USE CASE
The following three genes have been associated with gastric carcinoma:
ENSG00000141736
ENSG00000141510
ENSG00000132356

QUESTIONS
a) "How can I find out all diseases (besides gastric carcinoma) associated with those three Ensembl gene IDs?"

b) "Which diseases have got the highest overall association score for each of those three genes?"

c) Can I download the above list in TAB format?"

Interested in other use cases using our REST API? Check our blog posts.

QUICK GUIDE TO DATABASES

Here is a list of databases and projects that may be useful for you to explore:

PROTEINS

UniProtKB – The "Protein knowledgebase" is a comprehensive set of protein sequences. It is divided into two parts: TrEMBL and Swiss-Prot. The later is manually annotated and reviewed, therefore provides a set of protein sequences of high quality.

http://www.uniprot.org/

GENE NOMENCLATURE COMMITTEES

HGNC – The HUGO Gene Nomenclature Committee assigns unique names and symbols to every single human gene, whether they are coding or not. These gene names and symbols are the official ones for human genes.

http://www.genenames.org/

MGI – The HGNC counterpart for naming mouse genes and symbols.

http://www.informatics.jax.org/

GENETIC VARIANTS and SOMATIC MUTATIONS

GWAS catalog– The catalog of Genome Wide Association Studies (GWAS) provides genetic variants (e.g. SNPs) that are associated with a disease.

https://www.ebi.ac.uk/gwas/

EVA – The European Variation Archive (EVA) provides genetic variants and somatic mutations (associated with cancer).

https://www.ebi.ac.uk/eva/

Cancer Gene Census – A catalogue of genes for which mutations have been causally implicated in cancer. The Catalogue of Somatic Mutations in Cancer (COSMIC) at the Wellcome Trust Sanger Institute provides us with the set of genes associated with specific cancers in the Cancer Gene Census, in addition to other cancers associated with that gene in the COSMIC database.

www.cancer.sanger.ac.uk/census/

IntOGen - It provides evidence of somatic mutations, genes and pathways involved in tumorigenesis from 6,792 samples across 28 cancer types.

https://www.intogen.org/search

Gene2Phenotype - The data in Gene2Phenotype (G2P) provides evidence of genetic variants that are manually curated from the literature by consultant clinical geneticists in the UK. This is provided by DECIPHER, a database of genomic variants and phenotypes in patients with developmental disorders.

https://www.ebi.ac.uk/gene2phenotype

DRUGS

ChEMBL - The ChEMBL database at the EMBL-EBI provides evidence from known drugs that can be linked to a disease and a known target.

https://www.ebi.ac.uk/chembl/

RNA EXPRESSION

Expression Atlas – The Expression Atlas at EMBL-EBI provides information on genes that are differentially expressed between normal and disease samples, or among disease samples from different studies. In addition to differential expression, they provide baseline expression information for each gene.

https://www.ebi.ac.uk/gxa/home

AFFECTED PATHWAYS

Reactome – The Reactome database at the EMBL-EBI contains pathway information on biochemical reactions sourced from manual

curation. It identifies reaction pathways that are affected by pathogenic mutations.

http://www.reactome.org/

ANIMAL MODELS

Phenodigm - The Phenodigm resource at the Wellcome Trust Sanger Institute provides evidence on associations of targets and disease. It uses a semantic approach to map between clinical features observed in humans and mouse phenotype annotations.

http://www.sanger.ac.uk/resources/databases/phenodigm/

TEXT MINING

Europe PMC - The Europe PubMed Central at the EMBL-EBI mines the titles, abstracts and full text research articles from both PubMed and PubMed Central to provide evidence of links between targets and diseases.

http://europepmc.org/