Topic 8. Phenotypes and Diseases

4.1 Open Targets & InterMine practicals

Open Targets and InterMine practicals

This practical will introduce you to the data content and query functionality of **Open Targets** and **InterMine** through 2 different exercises:

1. **Open Targets:** Renal Cell Carcinoma (papillary) and the *MET* gene. Based on *"Open Targets Platform. Analysis and visualisation for early drug discovery. Coursebook"*, by Denise Carvalho-Silva.
2. **InterMine:** Diabetes and the *PPARG* gene.

Answers to the exercises are revised as of November 14th 2023.

Exercise 1. Open Targets: Renal Cell Carcinoma (papillary) and the *MET* gene

Scenario

This tutorial will guide you through the **Open Targets** website using **renal cell carcinoma** as an example, and exploring the ***MET*** gene, based on *'Reconstruction of a Functional Human Gene Network, with an Application for Prioritizing Positional Candidate Genes'* by Franke *et al.* AJHG 2006.

The following points will be addressed during the walkthrough:

- How to find targets associated with renal cell carcinoma
- How to filter down the number of targets based on specific evidence
- How to find the data sources used to support the target-disease association
- How to look for other diseases (than renal cell carcinoma) 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

Task

Use **Open Targets** (https://platform.opentargets.org/) to find targets associated with renal cell carcinoma in humans.

Directions

1. Go to https://platform.opentargets.org/ and search for *renal cell carcinoma*.
2. Select the first (Top) hit.
3. Go to the "Associated Targets" tab

Question to answer below

What is the total number of targets associated with renal cell carcinoma? **7025**

Task

Identify the target that shows the highest association with renal cell carcinoma and the data types that support this association.

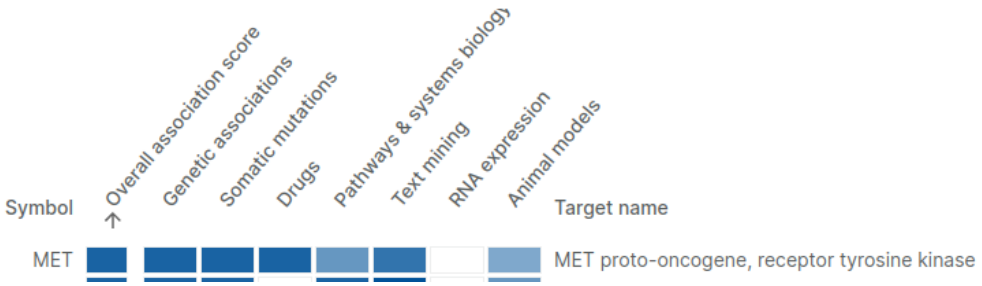
Directions

Have a look at the genes table. These are targets associated with renal cell carcinoma. The table is sorted by default with the best hit on the top of the table. 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: *Genetic association = Somatic mutations = drugs = pathways > RNA expression > Animal models > Text mining* (lowest weight of all data types).

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 combined to give the overall score ('Association score' column).

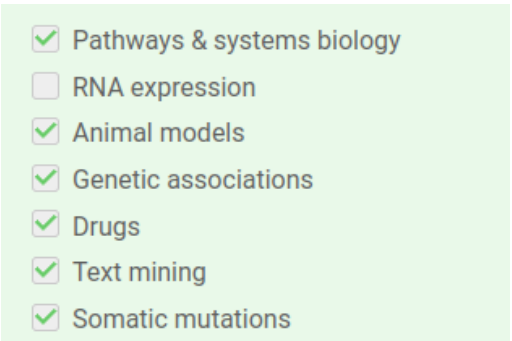
Question to answer below

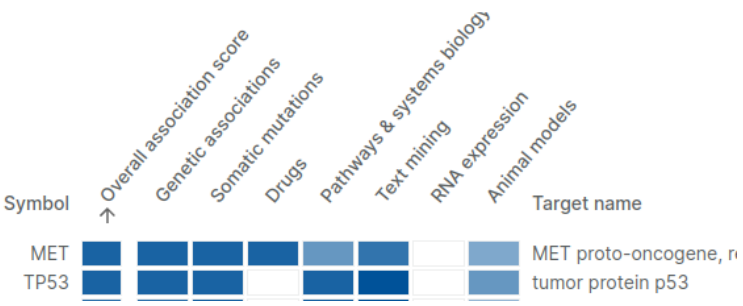
Which is the target that shows the highest association with renal cell carcinoma? MET



Question to answer below

What data types are supporting this association?





Task

Let's now explore the evidence used to associate *MET* and renal cell carcinoma.

Directions

1. Click on the name of the gene (*MET*) in the genes table.

2. Explore the resulting page "Evidence for MET in renal cell carcinoma". All the different sections detail the data that support the association.
3. Are there SNPs supporting the association according to ClinVar? What kind of functional consequence do they have (e.g. intronic, missense, etc.)?
4. Find out if there are drugs currently in clinical trials in patients with renal cell carcinoma.

Question to answer below
Which drugs are currently in **Phase III** for renal cell carcinoma? (enter their names separated by spaces)
SAVOLITINIB CABOZANTINIB

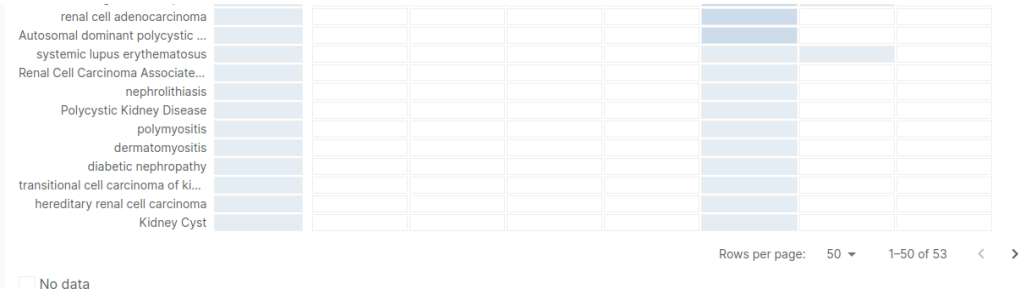
renal cell carcinoma	MET? and 1 other target	CABOZANTINIB	Small molecule	Hepatocyte growth factor receptor inhibitor and 1 other MoA	Phase III
renal cell carcinoma	MET? and 1 other target	CABOZANTINIB	Small molecule	Hepatocyte growth factor receptor inhibitor and 1 other MoA	Phase III
renal cell carcinoma	MET? and 1 other target	CABOZANTINIB	Small molecule	Hepatocyte growth factor receptor inhibitor and 1 other MoA	Phase III
renal cell carcinoma	MET? and 1 other target	CABOZANTINIB	Small molecule	Hepatocyte growth factor receptor inhibitor and 1 other MoA	Phase III
renal cell carcinoma	MET? and 1 other target	CABOZANTINIB	Small molecule	Hepatocyte growth factor receptor inhibitor and 1 other MoA	Phase III
papillary renal cell carcinoma	MET?	SAVOLITINIB	Small molecule	Hepatocyte growth factor receptor inhibitor	Phase III
renal cell carcinoma	MET?	SAVOLITINIB	Small molecule	Hepatocyte growth factor receptor inhibitor	Phase III
renal cell carcinoma	MET? and 1 other target	CABOZANTINIB	Small molecule	Hepatocyte growth factor receptor inhibitor and 1 other MoA	Phase III

Task
Explore this target (*MET*) in more detail, such as to find out its normal RNA expression levels across several tissues.

Directions
1. Scroll back to the top of the page and click on the "MET" link
2. Explore the resulting page "MET"
3. Scroll to the "Molecular interactions" section to see if MET interacts with a large network of other proteins or not.
4. Scroll to the "Baseline expression" section to find out in which tissues *MET* is highly expressed. Is *MET* expressed specifically in one or a few tissues, or does it show a broad expression over a wide range of tissues?
5. Scroll back to the top of the page and click on the tab "Associated diseases" (below the name of the gene) to find out all diseases associated with the *MET* (apart from renal cell carcinoma). There are three different displays that can be used to view the diseases associated with any given target:

- Table view: Diseases are listed in a table, ordered by the association score, which is colour coded in different shades of blue (strongest association is coloured in dark blue). The score varies from 0 to 1. When there is no evidence to support the association, the cells in this table are coloured in white (score of zero). Hover over the cells in the table to view the numbers. 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).
- Bubbles view: Diseases are grouped 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.
- Graph view: You can visualize the evidence across the therapeutic areas in a tree format that represents the relationships of diseases. Therapeutic areas have a square symbol, while diseases are represented as circles. The squares and circles are colour coded in blue, and the darker the blue, the stronger the association.

Question to answer below
How many diseases of the urinary system ("*Urinary system disease*") are associated with this target? (one of those should be renal cell carcinoma!) (Tip: Click on "Therapeutic Areas" at the left menu) **53**



Exercise 2. InterMine: Diabetes and the *PPARG* gene

Scenario
This tutorial will guide you through the InterMine website using diabetes as an example, and exploring the *PPARG* gene.

The following points will be addressed during the walkthrough:

- **Finding information about a specific gene (*PPARG*)**
- **Creating a list of genes associated with a disease (diabetes)**
- **Running template searches**
- **Performing more complex queries by using the query builder**
- **Intersecting lists**

Task
Use InterMine (http://intermine.org/) to find the gene *PPARG* in humans.

Directions
1. Go to the InterMine entry page: http://intermine.org/
2. Click the link HumanMine: http://www.humanmine.org/humanmine
3. Enter "PPARG" in the query box.
4. Human *PPARG* is among the first gene results returned. Click on this gene (Gene; Organism: *Homo sapiens*; Symbol: *PPARG*) to be taken to the report.
5. Explore the report page for this gene to find out:

- **On which chromosome is *PPARG* located? (Tip: Summary)**
- **Can you access the sequence of this gene? (Tip: Summary)**
- **With which diseases is *PPARG* associated? (Tip: Disease => Diseases)**
- **In which tissues is *PPARG* most highly expressed? (Tip: Expression => Rna Seq Results / Human Tissue Expression Visualizer)**
- **Does the PPARG protein have any known isoforms? (Tip: Proteins => Proteins)**
- **Is there an orthologue for *PPARG* in *D. melanogaster*? (Tip: Right menu => Other mines => FlyMine)**

Question to answer below: Which of the following is NOT a disease associated with the *PPARG* gene?