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Topic 8. Phenotypes and Diseases Activity

In the beginning, life looked rosy for thalidomide. Advertised under the names "Distaval" and "Thalomid", this drug came about when a failed anti-allergy drug proved to be somewhat of a wonder cure for people suffering from anxiety disorders. These included morning sickness, which in the swinging 60's was seen to be a result of stress. Unknowing, thousands of mothers were taking thalidomide pills to combat their morning sickness and dizziness, blissfully unaware of what was going on with their poor foetuses. The shock came when the children were born with normal head and trunk but with shortened or no limbs. After the foetal damage, thalidomide soon went out of vogue. It was put on the shelf for years after the dangers became apparent, and it was only when a doctor in Israel was searching for a cure to the horrible disease leprosy that thalidomide was considered. Thalidomide was then found to be something of an immune system regulator, and was used to treat certain immune system diseases. One of the success stories was that of Sarah Craven, who suffered from Behcet's disease. Sarah Craven was lucky to have been given thalidomide, as within three weeks, the ulceration caused by Behcet's disease cleared up completely on both her tongue and genitals. She soon became healthy enough to have a child, and staved off thalidomide for the first five months of pregnancy so as not to damage the unformed fetus. Sadly, Behcet's symptoms soon came back, and by the sixth month of her pregnancy, she had to take the drug again. Nothing happened to Sarah Craven's child at all, and she now has a healthy son named Jake. After being used to treat leprosy and Behcet's disease, the life of thalidomide suddenly got a lot more interesting. While treating cancer sufferers, it was found that thalidomide could help to kill solid tumors within the body by preventing angiogenesis. After all of the positive attributes of thalidomide came to light, many companies tried to make the drug safer. Celgene has manufactured "Revomid". This drug was created by altering the make up of thalidomide, producing a pill that is far safer to use, and also more effective.

1. **Use OMIM or Open Targets to investigate about Leprosy and Behcet’s disease:**

    a. **Summarize what is leprosy disease**

    A chronic granulomatous infection caused by MYCOBACTERIUM LEPRAE. The granulomatous lesions are manifested in the skin, the mucous membranes, and the peripheral nerves. Two polar or principal types are lepromatous and tuberculoid.

    This disease is intricately linked to 752 target associations, with TNF superfamily member 15 (TNFSF15) as the most prominently associated target. The experimental models that support this association are genetic associations and text mining.

    Focusing on TNFSF15 gene, there are 327 diseases or phenotypes associated with this gene. The subcellular location of TNFSF15 is the nuclear membrane.

b. Summarize what is Behcet's disease

An autoimmune disease of the cardiovascular system and is_a vasculitis that causes chronic inflammation in blood vessels throughout the body leading to ulcerations on the mouth and sometimes the genitals, notorious for causing hypopyon uveitis.

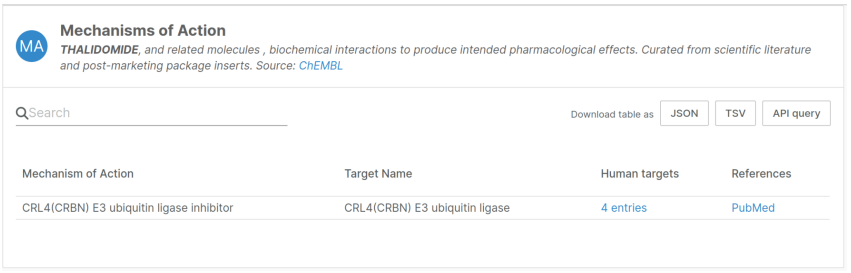
This disease is intricately linked to 735 target associations, with nucleotide binding oligomerization domain containing 2 (NOD2) as the most prominently associated target. The experimental models that support this association are genetic associations and text mining. Also, we can observe that drugs have a lower support.

Focusing on the NOD2 gene, there are 636 diseases or phenotypes associated with this gene. These candidates span different phases, with Phase II and Phase IV. Also, we have small molecules that are present in the stages of development of these candidates, this is MIFAMURTIDE. The subcellular location of NOD2 is in the cytosol and in the golgi apparatus.

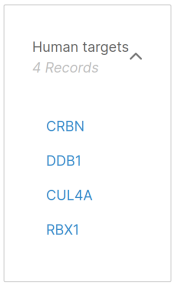
2. Use Open Targets to investigate about Thalidomide and answer the following questions:

a. Which are the targets of Thalidomide? (tip: query for "thalidomide" and find "Human targets" under the section "Mechanisms of Action")

The section 'Mechanism of actions' is the following:



More precisely, when checking the 4 entries in 'Human targets' we obtain:



Accordingly, the targets of Thalidomide are CRBN, DDB1, CUL4A and RBX1.

b. In which kind of diseases has Thalidomide shown to be effective? (tip: query for "thalidomide" and find "Indication" under the section "Indications")

If we get to the section "Indications" of Thalidomide the first 25 results we get are:

Indication	Therapeutic Areas	Max Phase ↓	Source
multiple myeloma	4 areas	Phase IV	121 entries
immune system disease	immune system disease	Phase IV	ATC
colorectal neoplasm	2 areas	Phase III	ClinicalTrials.gov
diffuse large B-cell lymphoma	4 areas	Phase III	2 entries
fallopian tube cancer	2 areas	Phase III	ClinicalTrials.gov
vascular malformation	3 areas	Phase III	ClinicalTrials.gov
peritoneum cancer	2 areas	Phase III	ClinicalTrials.gov
malignant epithelial tumor of ovary	3 areas	Phase III	ClinicalTrials.gov
extranodal nasal NK/T cell lymphoma	5 areas	Phase III	ClinicalTrials.gov
hepatocellular carcinoma	3 areas	Phase III	7 entries
AL amyloidosis	4 areas	Phase III	ClinicalTrials.gov
Hypoalbuminemia	phenotype	Phase III	ClinicalTrials.gov
kidney cancer	2 areas	Phase III	4 entries
cancer	cancer or benign tumor	Phase III	4 entries
Cough	phenotype	Phase III	ClinicalTrials.gov
colorectal carcinoma	2 areas	Phase III	ClinicalTrials.gov
Crohn's disease	3 areas	Phase III	4 entries
ulcerative colitis	3 areas	Phase III	ClinicalTrials.gov
lung cancer	2 areas	Phase III	6 entries
sarcoidosis	musculoskeletal or connective tissue disease	Phase III	ClinicalTrials.gov
myelodysplastic syndrome	3 areas	Phase III	3 entries
neoplasm	cancer or benign tumor	Phase III	4 entries
colorectal adenocarcinoma	2 areas	Phase III	ClinicalTrials.gov
idiopathic pulmonary fibrosis	2 areas	Phase III	2 entries
kidney neoplasm	2 areas	Phase III	ClinicalTrials.gov

As it can be seen, Thalidomide has shown to be effective in diseases belonging to different therapeutic areas (e.g. "genetic, familial or congenital disease", "cancer or benign tumor", "immune system disease", "hematologic disease"). Also, the phase in which their clinical trials are is not the same for all diseases. If we search for clinical trials at stage IV (completed) we see that there are 2, showing that Thalidomide is effective in multiple myeloma and immune system disease.

3. Use the Open Targets and HumanMine to investigate about the targets you identified in the previous question (tip: create a list with all the identified targets):

a. To which key therapeutic areas do these targets belong?

CRBN: The main therapeutic area to which this target below is the genetic, familial or congenital disease.

DDB1: The main therapeutic area to which this target below is the cancer or benign tumor.

CUL4A: The main therapeutic area to which this target below is the cancer or benign tumor.

RBX1: The main therapeutic area to which this target below is the cancer or benign tumor.

We can find these answers for this question when we look into the "Associated disease" section and then we click on the "Therapeutic areas" tab. There, we stick with the one that has the highest number.

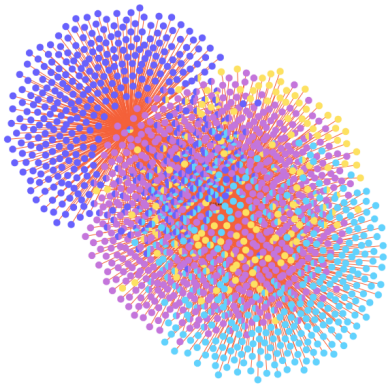
b. Which other drugs target the same genes (list just a few)?

Apart from THALIDOMIDE all these four genes also target the following drugs: LENALIDOMIDE and POMALIDOMIDE.

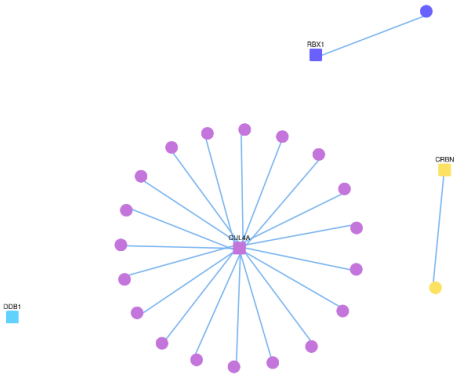
We can find this when we look into the "Known drugs" section for each of the targets.

c. Do these genes interact physically? Do they interact genetically?

Create a list (upload) in Human Mind (put the identifiers) and then use templates.



Physical interaction



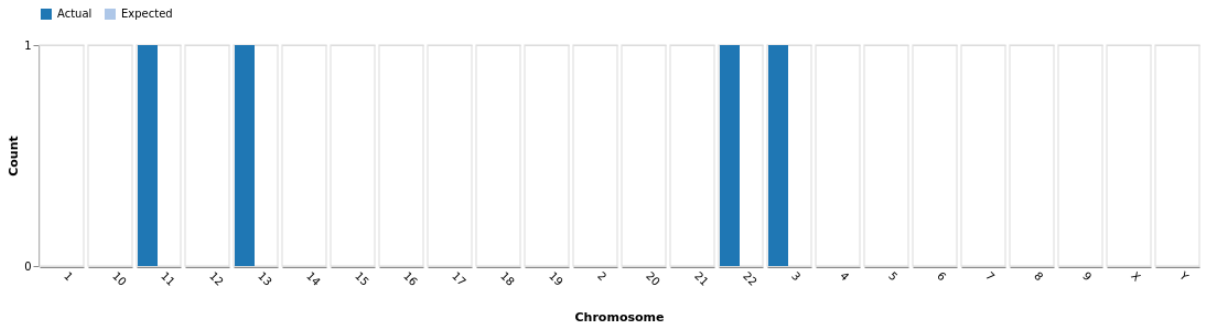
Genetic interaction

In the first picture above, we can clearly say that there's a physical interaction between all these genes.

However, as we can see in the second picture, they are more dispersed which means that there's no genetic interaction between them.

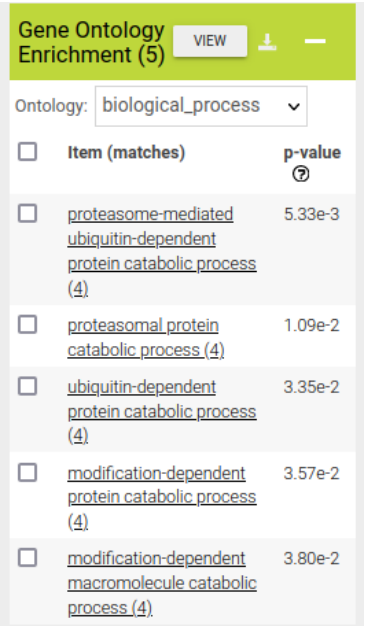
d. Are all these genes located in the same chromosome?

No, in this image, we can see that each gene is located on a different chromosome.



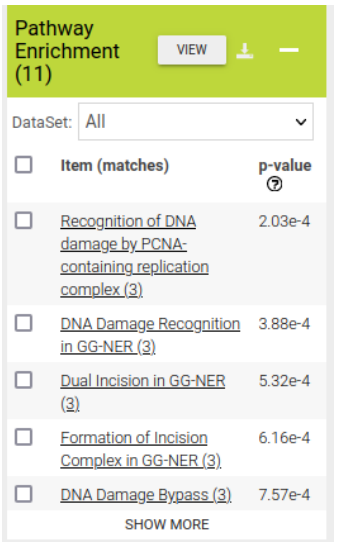
e. Are there Gene Ontology terms enriched in this list of target genes?

Yes, there are 5 Gene Ontology terms enriched in this list.



f. Are there pathways enriched in this list of target genes?

Yes, there are 11 pathways enriched in this list of target genes.



4. Finally, focus on the gene CUL4A and use HumanMine to investigate about this gene:

a. Is the gene differentially expressed under any condition?

For down regulated, we have the following conditions (5 rows):

Atlas Expression T Statistic	Atlas Expression Type	Atlas Expression Condition	Atlas Expression Expression	Atlas Expression P Value
-20.4	disease_state	Huntingtons disease	DOWN	0
-19.5	disease_state	multiple myeloma	DOWN	0
-15.9	disease_state	multiple myeloma	DOWN	0
-14.8	organism_part	brain caudate nucleus	DOWN	0
-11.9	disease_state	bipolar disorder	DOWN	1.4114754059871501e-30

And for up regulated, we have the following conditions (5 rows):

Atlas Expression T Statistic	Atlas Expression Type	Atlas Expression Condition	Atlas Expression Expression	Atlas Expression P Value
18.6	organism_part	skeletal muscle	UP	0
17.6	organism_part	cervix	UP	0
17.1	disease_state	cervical carcinoma	UP	0
12.6	organism_part	skeletal muscle	UP	3.8551503546018125e-34
11.8	disease_state	colorectal adenocarcinoma	UP	6.192563296967996e-30

b. Do fruit flies have this gene in their genomes? What is its name?

Homology

Homologues (6)

Showing 1 to 6 of 6 rows OPTIONS Rows per page: All (6) Page 1

Homologues Type	Gene Primary Identifier	Homologue Primary Identifier	Organism Short Name
least diverged orthologue	8451	FBgn0033260	D. melanogaster
least diverged orthologue	8451	MGI:1914487	M. musculus
least diverged orthologue	8451	RGD:1563853	R. norvegicus
least diverged orthologue	8451	S000003583	S. cerevisiae
least diverged orthologue	8451	WBGene00000839	C. elegans
least diverged orthologue	8451	ZDB-GENE-040426-1357	D. rerio

We can observe that D.melanogaster (fruit flies) have this gene in their genome. The homologue primary identifier is FBgn0033260.