

# Materials

- Slides



- Coursebook



[www.github.com/deniseOme/training/](https://www.github.com/deniseOme/training/)

# Open Targets: integrating genetics, omics and chemistry for drug discovery

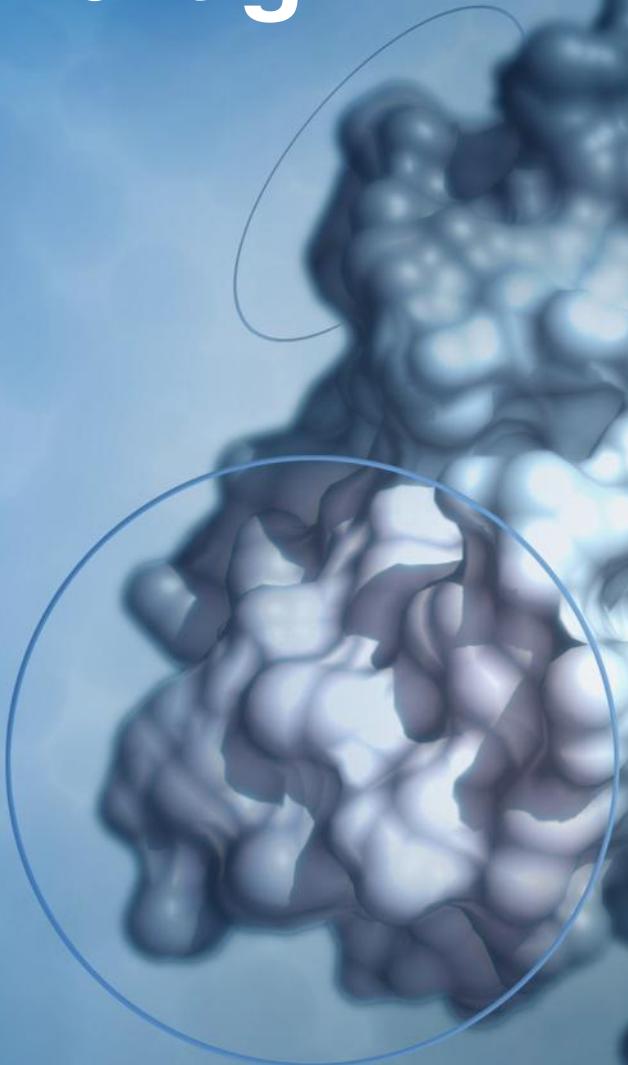
Osong Medical Innovation Foundation  
New Drug Development Center  
October 18<sup>th</sup> 2018

**Dr Denise Carvalho-Silva**

Open Targets / EMBL-EBI  
Wellcome Genome Campus  
United Kingdom



Open Targets



# Aims of this workshop



What is Open Targets?

What can you use the  
Open Targets Platform for?

Other ways to  
access the data

How to get  
in touch

# Today: 10:00-16:00

- Introduction
- Open Targets Platform: live demos
- Exercises
- Other modes of data access
- Feedback survey and wrap up

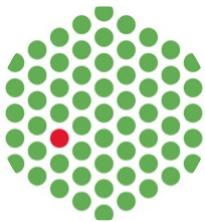
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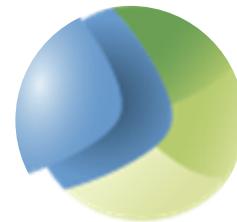
# Open Targets

<https://www.opentargets.org>

A partnership to transform drug discovery  
through the systematic identification and  
prioritisation of targets



2014



2016



2017

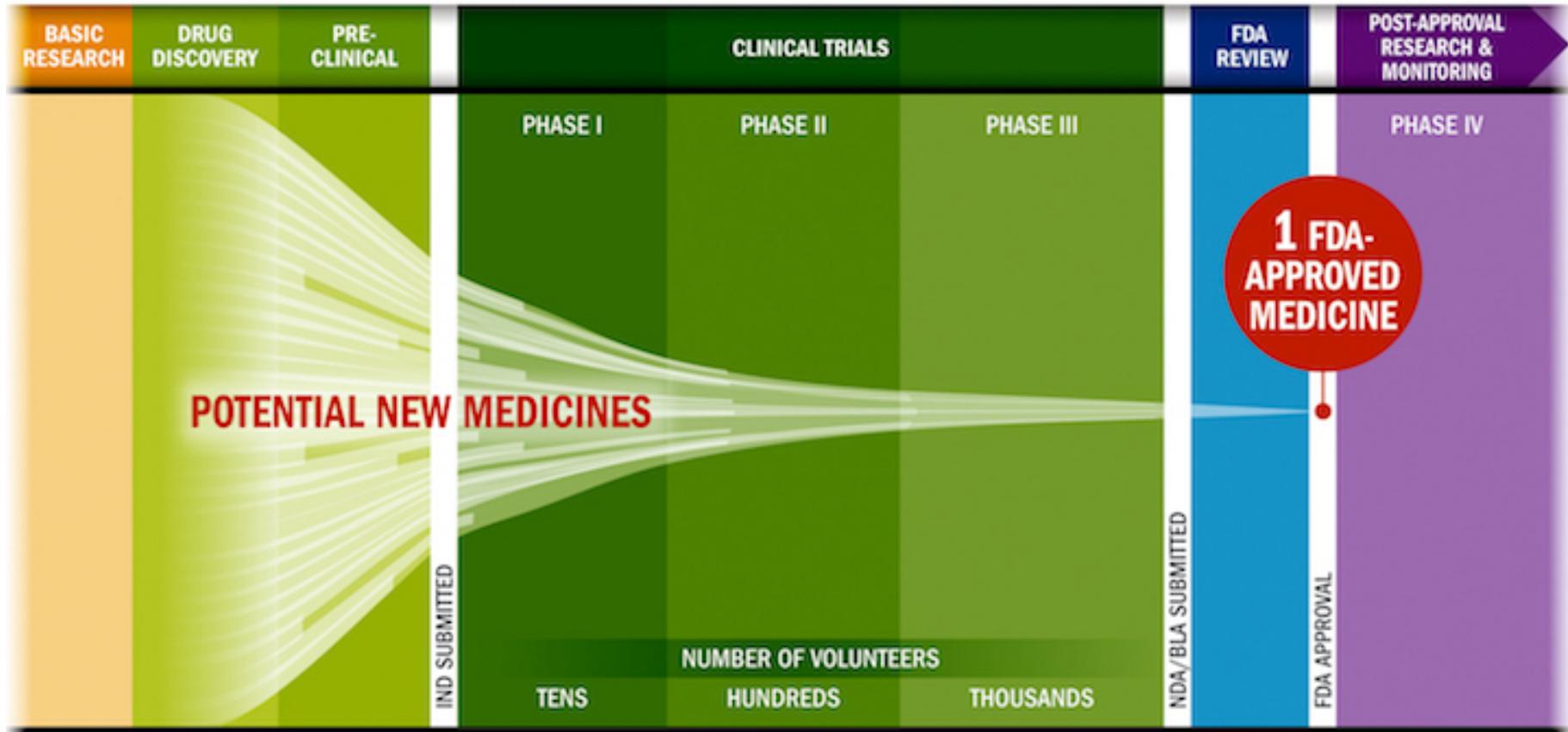


2018



Open Targets

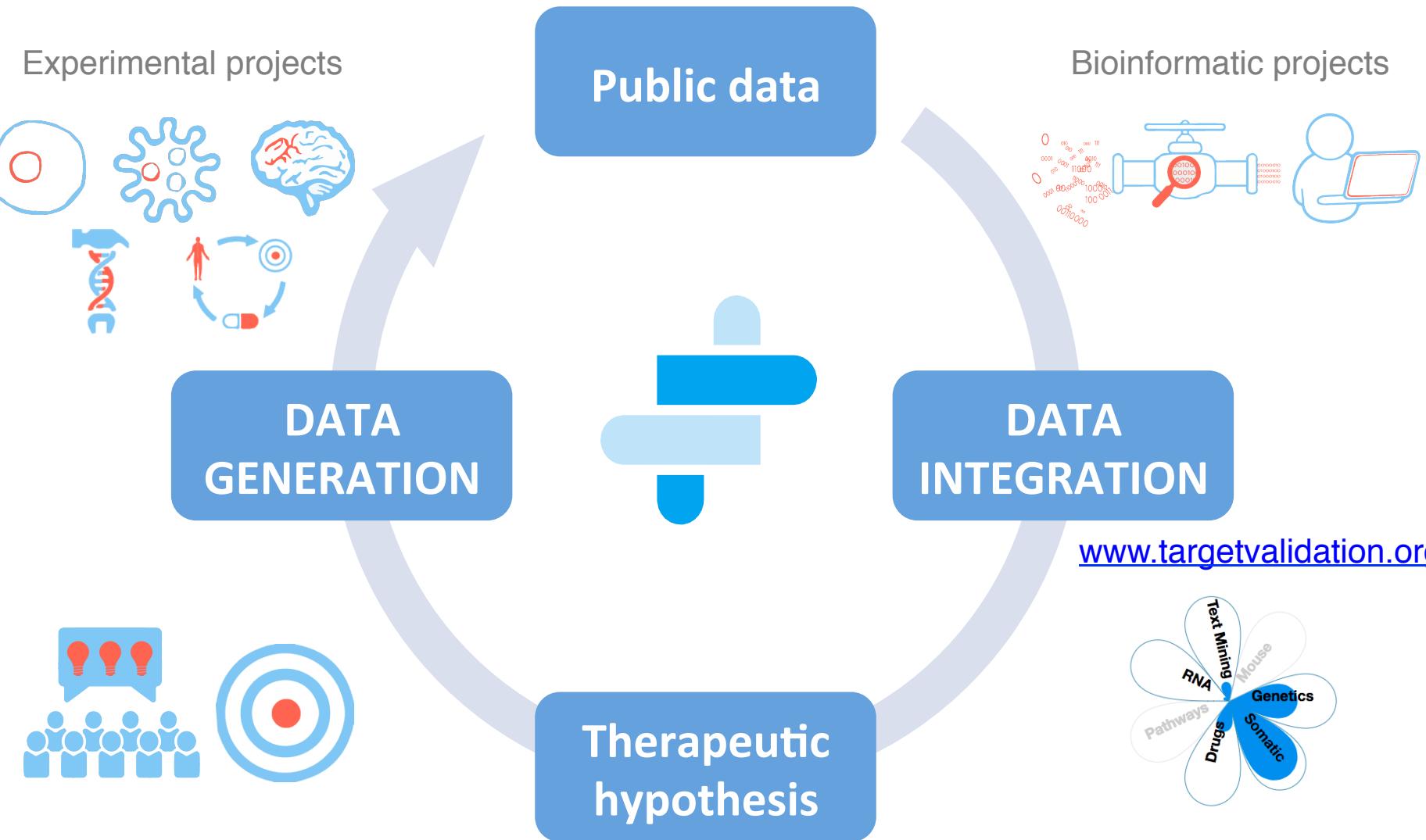
# Drug discovery: some challenges



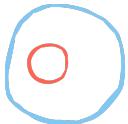
Lengthy, costly, low success rate, **HIGH ATTRITION RATES**

Source: PhRMA adaptation based on Tufts CSDD & School of Medicine, and FDA

# Virtuous cycle in Open Targets



# Data generation: Open Targets



- > 1,000 cancer cell lines + drug sensitivity data
- RNASeq, CRISPR/Cas9 screens
- Wellcome Sanger Institute, GSK and EMBL-EBI



- Genome wide knockouts in gut epithelium
- Organoids, metagenomics
- Wellcome Sanger Institute and GSK



- Alzheimer's and Parkinson's
- CRISPR/Cas9 screens, iPS cells
- Wellcome Sanger Institute, Biogen, Gurdon Institute



Open Targets

# Reasons for data integration

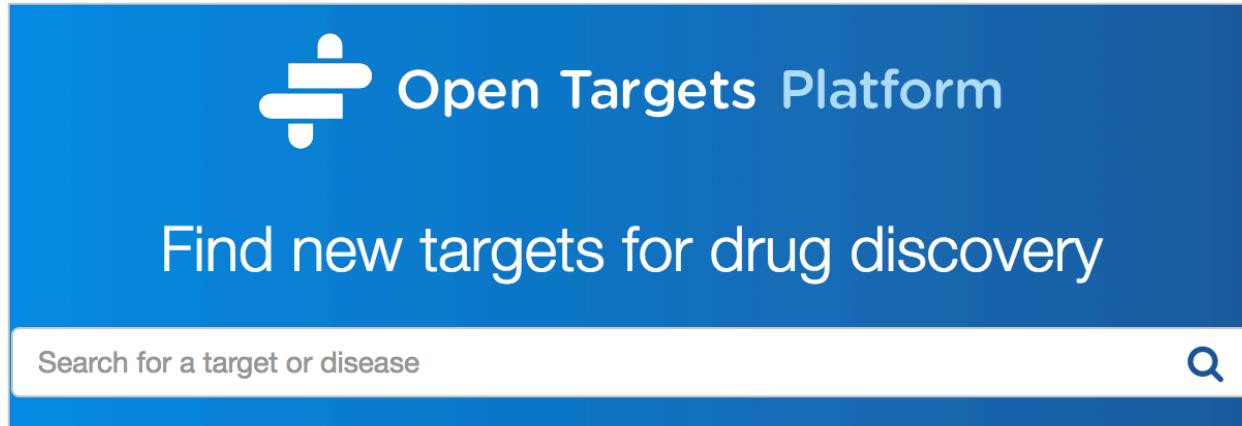


- Data is everywhere
- Fit everything together: time
- Possible lack of resources or expertise

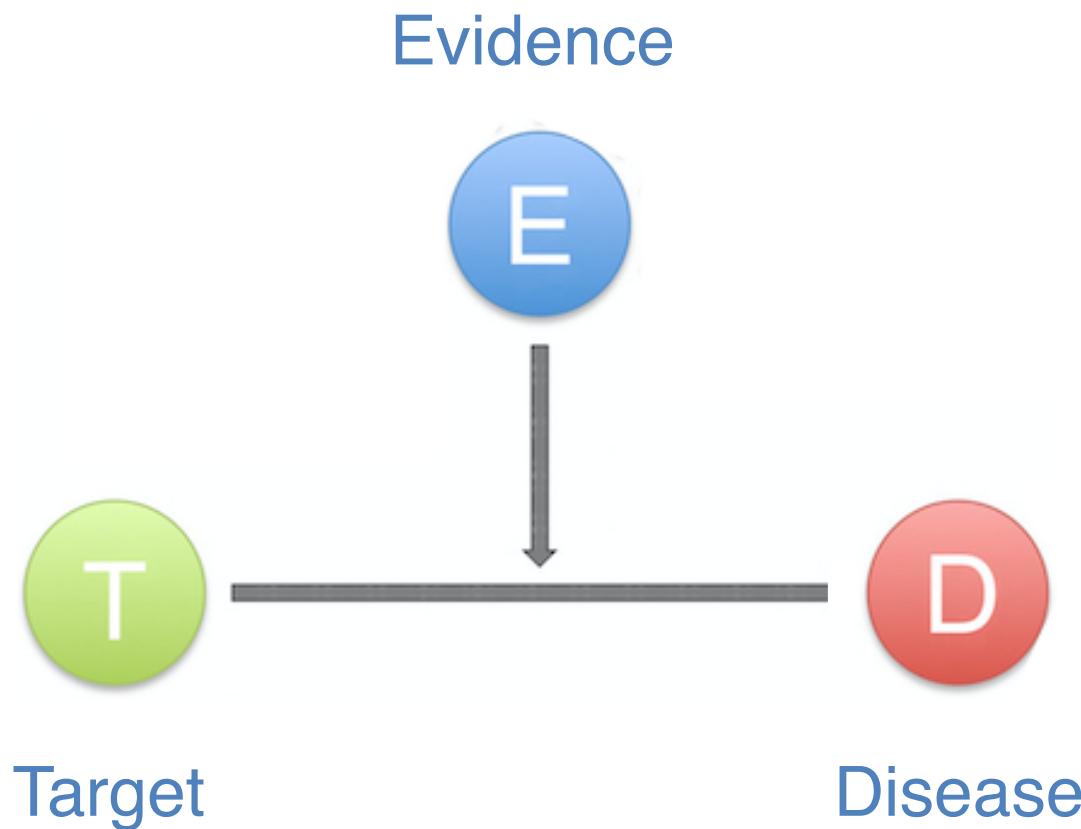
# Data integration: Open Targets

- Open Targets Platform
- Several databases in a single place
- Freely available: disease biology, drug discovery, translational





The image shows the Open Targets Platform homepage. At the top left is the platform's logo, which consists of a stylized white 'T' and 'O' icon followed by the text 'Open Targets Platform'. Below the logo is a blue header bar with the text 'Find new targets for drug discovery'. Underneath the header is a search bar containing the placeholder 'Search for a target or disease' and a magnifying glass icon.

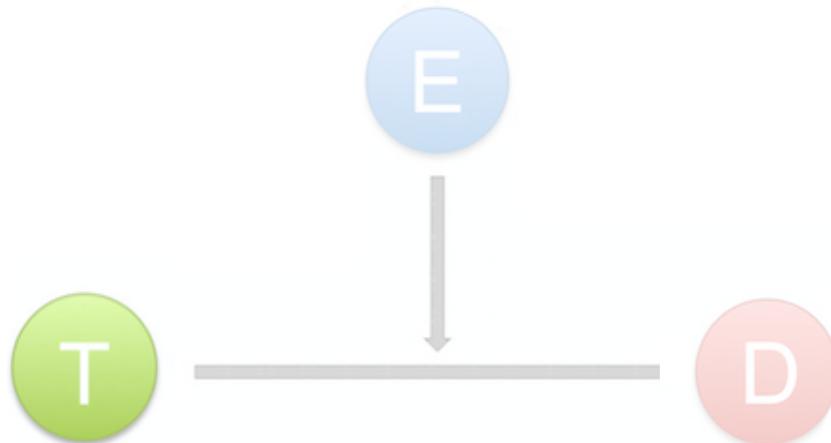


# Targets → genes (coding or not)

- HGNC names e.g. DMD (synonyms)
- Ensembl Gene IDs e.g. ENSG00000105641
- UniProt IDs e.g. P15056
- Non-coding genes e.g. MIR100HG

21K  
targets

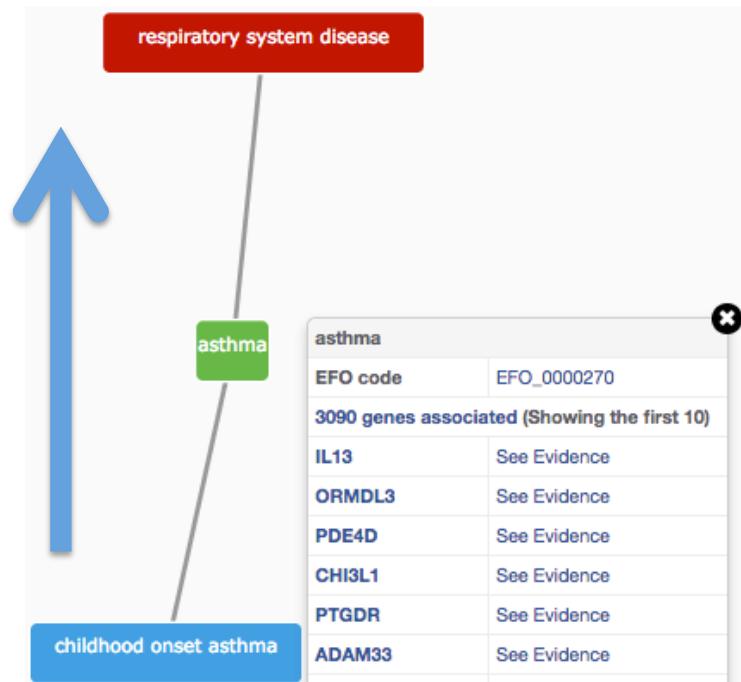
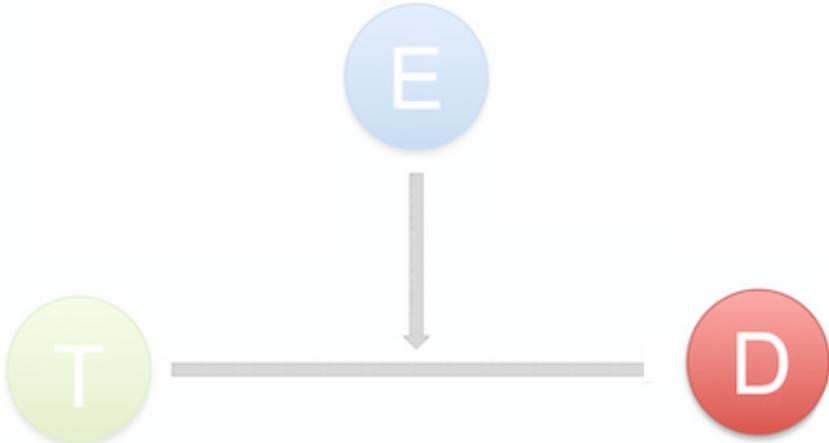
<https://docs.targetvalidation.org/faq/what-is-a-target>



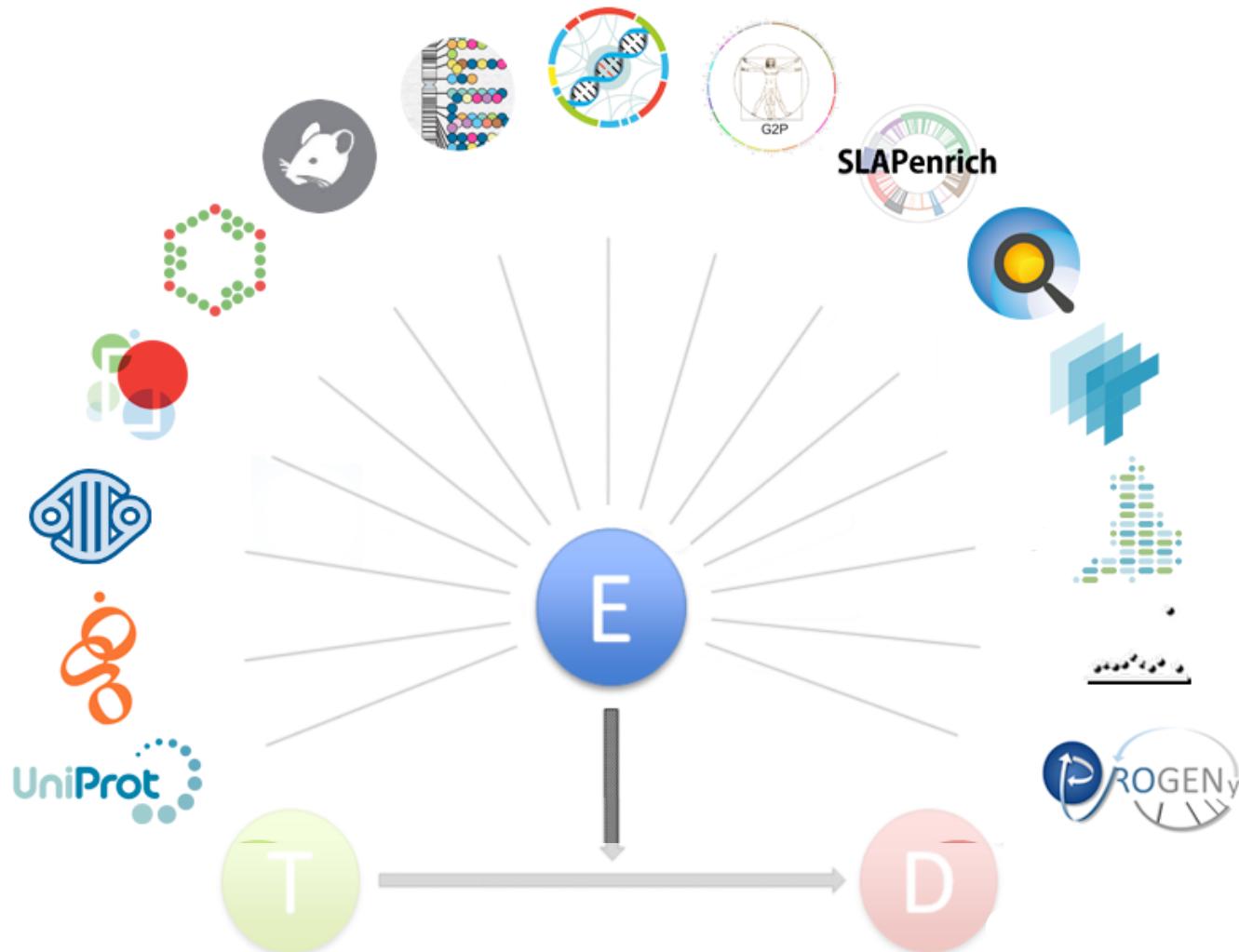
# Diseases, and phenotype

10K  
diseases

- Modified version of Experimental Factor Ontology (EFO)
- Controlled vocabulary (Alzheimers versus Alzheimer's)
- Hierarchy (relationships)
  - Promotes consistency
  - Increases the richness of annotation
  - Allow for easier and automatic integration



# Evidence for our T-D associations



<https://docs.targetvalidation.org/data-sources/data-sources>

# What can you use the Open Targets Platform for?



1) Target-disease associations (+ evidence + score)

[https://www.targetvalidation.org/evidence/ENSG00000141510/EFO\\_0000228](https://www.targetvalidation.org/evidence/ENSG00000141510/EFO_0000228)

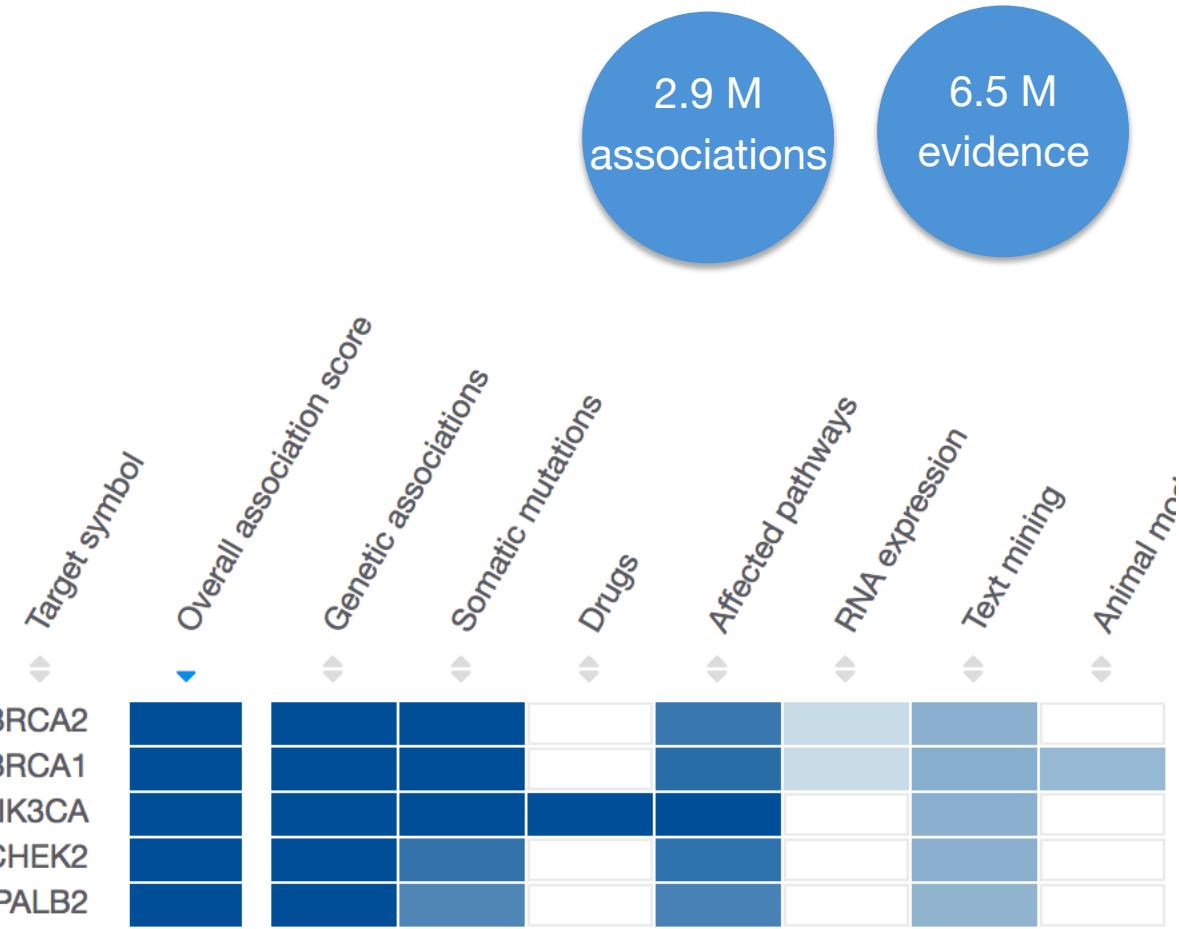
2) Disease annotations

[http://www.targetvalidation.org/diseaset/EFO\\_0000228](http://www.targetvalidation.org/diseaset/EFO_0000228)

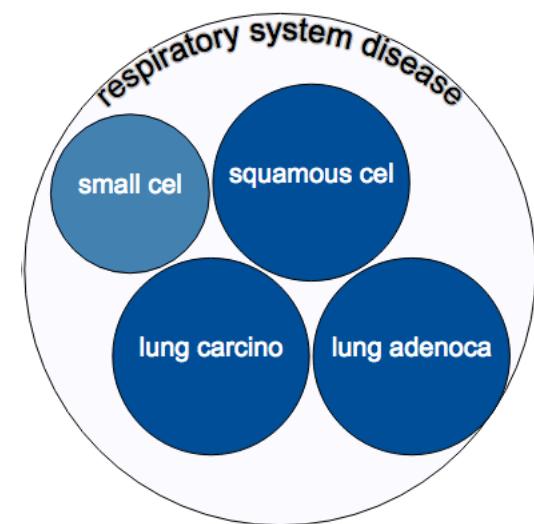
3) Target annotations

<http://www.targetvalidation.org/target/ENSG00000141510>

# 1) Target-disease associations

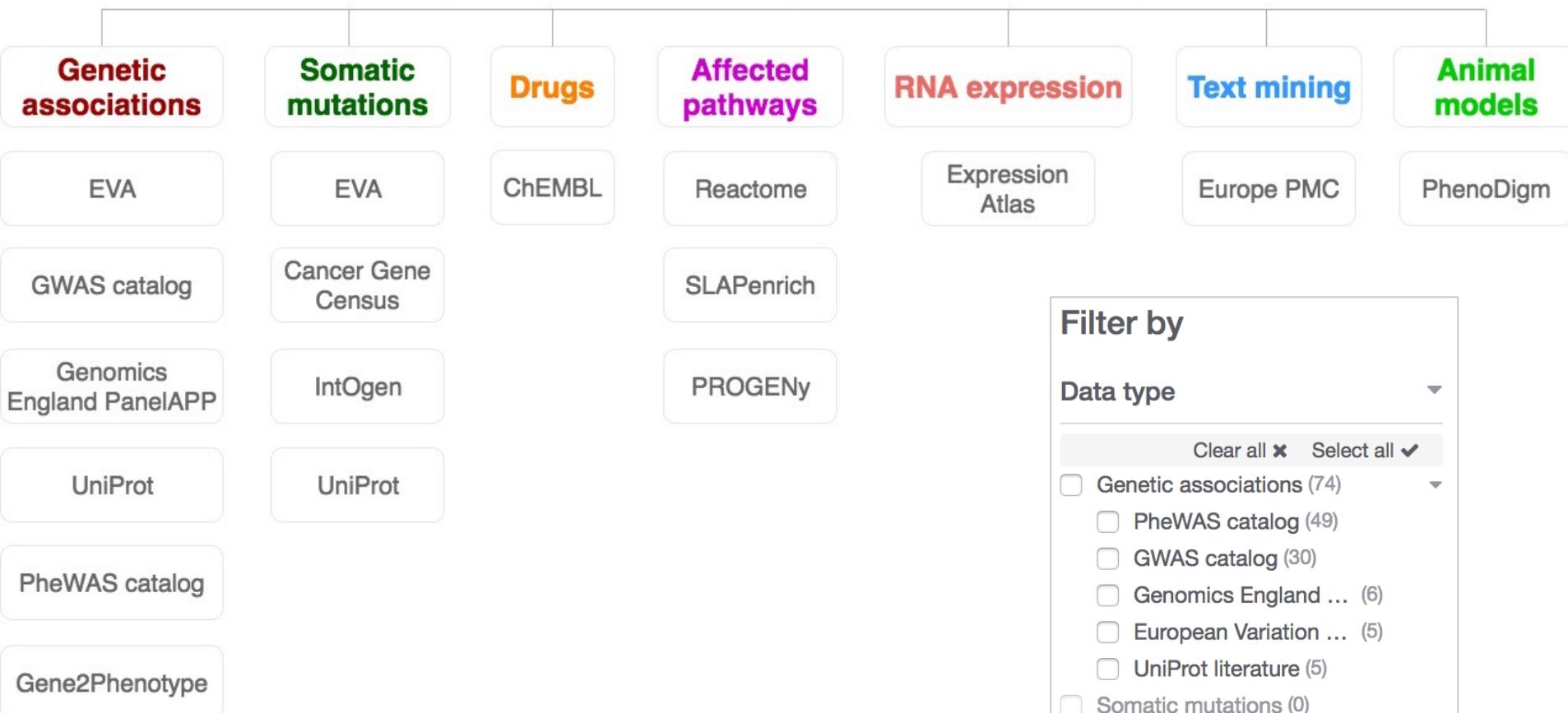


Targets associated  
with breast carcinoma



Diseases associated  
with BRCA2

# Data sources grouped into data types



## Filter by

### Data type

Clear all  Select all

- Genetic associations (74)
  - PheWAS catalog (49)
  - GWAS catalog (30)
  - Genomics England ... (6)
  - European Variation ... (5)
  - UniProt literature (5)
- Somatic mutations (0)
- Drugs (30)
- Affected pathways (21)
- RNA expression (4)
- Text mining (99)
- Animal models (45)

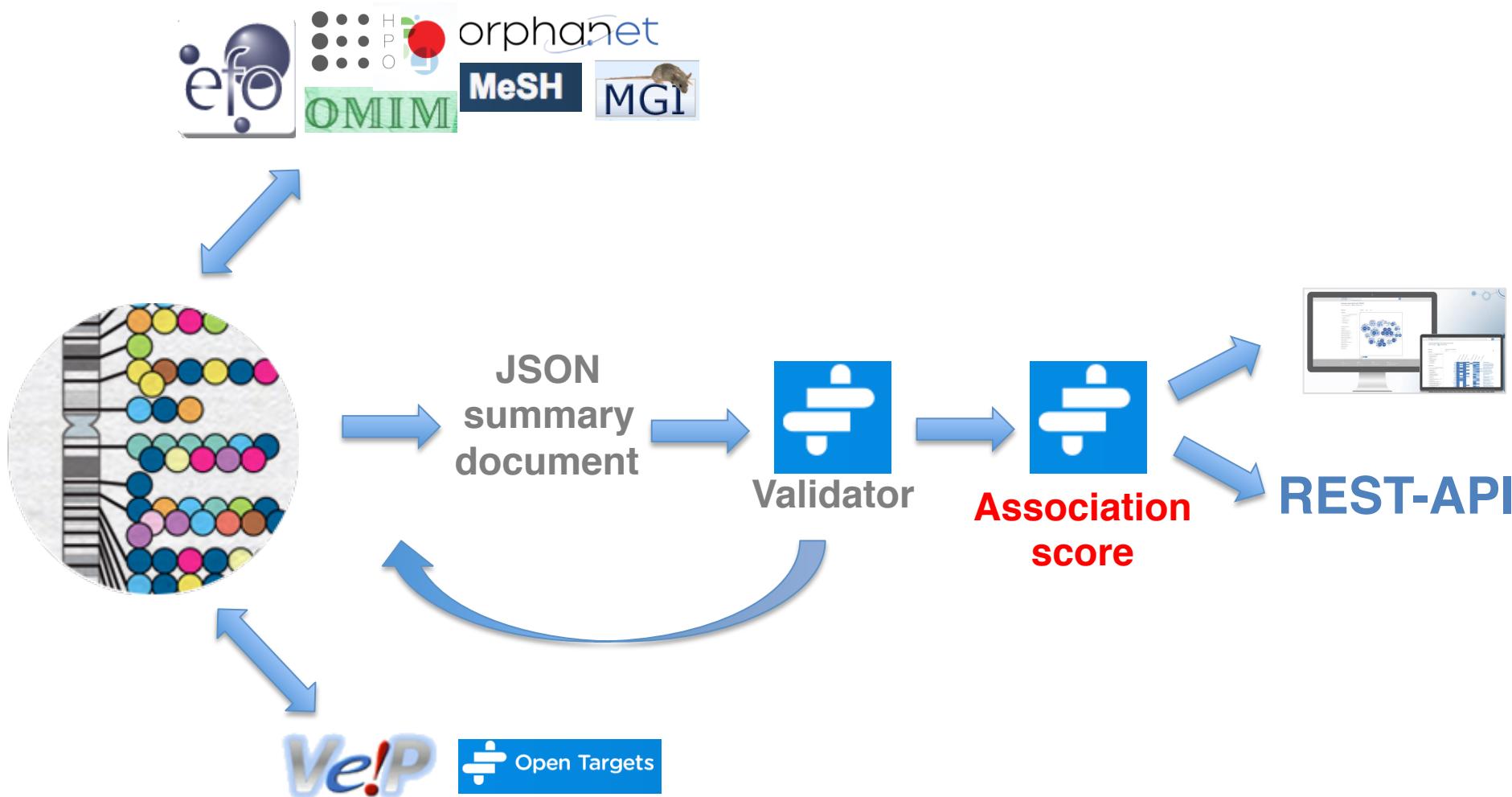
# JSON summary document

```
"7","target":"http://identifiers.org/ensembl/ENSG00000012048","object":"http://www.ebi.ac.uk/efo/EF0_0004704","variant":"http://identifiers.org/dbsnp/rs1799949","study_name":"otar009_gwas_catalog","pvalue":"8e-11","confidence_interval":"0.1-0.18","odd_ratio":""}]},"evidence": {"variant2disease": {"gwas_sample_size": 69626, "unique_experiment_reference": "http://europepmc.org/abstract/MED/26414677", "gwas_panel_resolution": 2600000, "provenance_type": {"literature": {"references": [{"lit_id": "http://europepmc.org/abstract/MED/26414677"}]}}, "expert": {"status": true, "statement": "Primary submitter of data"}, "database": {"version": "2018-07-03T08:28:14+00:00", "id": "GWAS Catalog", "dbxref": {"version": "2018-07-03T08:28:14+00:00", "id": "http://identifiers.org/gwas_catalog"}}, "is_associated": true, "source_score": {"type": "pvalue", "method": {"description": "pvalue for the SNP to disease association."}, "value": 8e-11}, "evidence_codes": ["http://identifiers.org/eco/GWAS", "http://purl.obolibrary.org/obo/ECO_0000205"], "date_asserted": "2018-07-03T08:28:14+00:00"}, "genotype": {"variant": {"provenance_type": {"expert": {"status": true, "statement": "Primary submitter of data"}, "database": {"version": "2018-07-03T08:28:14+00:00", "id": "GWAS Catalog", "dbxref": {"version": "2018-07-03T08:28:14+00:00", "id": "http://identifiers.org/gwas_catalog"}}, "is_associated": true, "date_asserted": "2018-07-03T08:28:14+00:00", "evidence_codes": ["http://purl.obolibrary.org/obo/ECO_0000205", "http://identifiers.org/eco/cttv_mapping_pipeline"], "functional_consequence": "http://purl.obolibrary.org/obo/SO_0001819"}, "validated_against_schema_version": "1.2.8", "type": "genetic_association", "literature": {"references": [{"lit_id": "http://europepmc.org/abstract/MED/26414677"}]}}}]},"target": {"activity": "http://identifiers.org/cttv.activity/predicted_damaging", "id": "http://identifiers.org/ensembl/ENSG00000012048", "target_type": "http://identifiers.org/cttv.target/gene_evidence", "access_level": "public", "sourceID": "gwas_catalog", "variant": {"type": "SNP single", "id": "http://identifiers.org/dbsnp/rs1799949"}, "disease": {"id": "http://www.ebi.ac.uk/efo/EF0_0004703"}, "unique_association_fields": {"sample_size": 140426, "gwas_panel_resolution": 532488, "pubmed_refs": "http://europepmc.org/abstract/MED/29773799", "target": "http://identifiers.org/ensembl/ENSG00000012048", "object": "http://www.ebi.ac.uk/efo/EF0_0004703", "variant": "http://identifiers.org/dbsnp/rs1799949", "study_name": "otar009_gwas_catalog", "pvalue": "3e-8", "confidence_interval": "0.099-0.205", "odd_ratio": ""}, "evidence": {"variant2disease": {"gwas_sample_size": 140426, "unique_experiment_reference": "http://europepmc.org/abstract/MED/29773799", "gwas_panel_resolution": 532488, "provenance_type": {"literature": {"references": [{"lit_id": "http://europepmc.org/abstract/MED/29773799"}]}}, "expert": {"status": true, "statement": "Primary submitter of data"}, "database": {"version": "2018-07-03T08:50:28+00:00", "id": "GWAS Catalog", "dbxref": {"version": "2018-07-03T08:50:28+00:00", "id": "http://identifiers.org/gwas_catalog"}}, "is_associated": true, "source_score": {"type": "pvalue", "method": {"description": "pvalue for the SNP to disease association."}, "value": 3e-8}, "evidence_codes": ["http://identifiers.org/eco/GWAS", "http://purl.obolibrary.org/obo/ECO_0000205"], "date_asserted": "2018-07-03T08:50:28+00:00"}, "genotype": {"variant": {"provenance_type": {"expert": {"status": true, "statement": "Primary submitter of data"}, "database": {"version": "2018-07-03T08:50:28+00:00", "id": "GWAS Catalog", "dbxref": {"version": "2018-07-03T08:50:28+00:00", "id": "http://identifiers.org/gwas_catalog"}}, "is_associated": true, "date_asserted": "2018-07-03T08:50:28+00:00", "evidence_codes": ["http://purl.obolibrary.org/obo/ECO_0000205", "http://identifiers.org/eco/cttv_mapping_pipeline"], "functional_consequence": "http://purl.obolibrary.org/obo/SO_0001819"}, "validated_against_schema_version": "1.2.8", "type": "genetic_association", "literature": {"references": [{"lit_id": "http://europepmc.org/abstract/MED/26414677"}]}}}]}
```



\* IDs (gene, variant, disease, papers) + evidence + source + stats for the score

# How does the data\* get integrated?



\* e.g. germline variants from GWAS Catalog

# Association score



Which targets have more evidence for an association with a disease?

What is the relative weight of the evidence for different targets?



# Four-tier scoring framework

## Statistical integration, aggregation and scoring

- 1) Evidence score (e.g. one SNP from a GWAS paper)
- 2) Data source score (e.g. all SNPs from the GWAS catalog)
- 3) Data type score (e.g. all sources of Genetic associations)
- 4) Overall association score

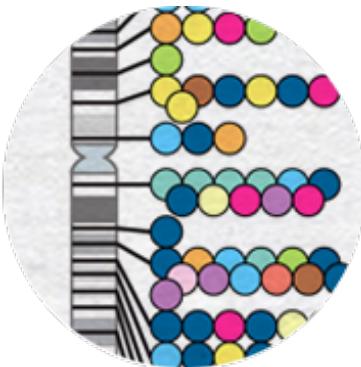
# Step 1: evidence score

$$score = f * s * confidence$$

f, relative occurrence of a target-disease evidence

s, strength of the effect of the variant

c, confidence of the observation for the target-disease evidence



f = sample size (cases and controls)

s = predicted functional consequence (VEP)

c = p value reported in the paper

(Factors affecting the relative strength of GWAS Catalog evidence)

## Factors affecting the relative strength of the evidence

Somatic mutations	Cancer Gene Census (functional consequence score of variants); European Variation Archive (functional consequence score of variants); IntOGen (binned score based on tumour type categories. If the gene has several signals of positive selections in the tumour, the score will be 0.25. If the gene is already described as a cancer gene and exhibits a signal of positive selection in a tumor type, the score will be 0.5. If in addition to a signal of positive selection, the gene is functionally connected to other genes in the same tumor type, the score will be 0.75)
Drugs	ChEMBL (Clinical trials phase binned score. Scores will be 0.09 for phase 0, 0.1 for phase I, 0.2 for Phase II, 0.7 for Phase III, and 1 for Phase IV drugs)
Affected pathways	Reactome (functional consequence of 1 for a pathway inferred by a curator). SLAPenrich evidence is scored according to <a href="#">Iorio F et al 2018</a> followed by quantifying, in large cohorts of cancer patients, the divergence of the total number of samples with genomic alterations in a Reactome-pathway from its expectation, accounting for mutational burdens and total exonic block lengths of genes in that pathway. PROGENy evidence is scored per sample and pathway following a modifications of the original implementation described by <a href="#">Schubert et al. 2016</a> . Further details can be found <a href="#">elsewhere</a> .
RNA Expression	Expression Atlas score (normalised p-value, normalised expression fold change and normalised percentile rank)
Text mining	Europe PMC (weighting document sections, sentence locations and title for full text articles and abstracts ( <a href="#">Kafkas et al 2016</a> ))
Animal models	<a href="#">PhenoDigm</a> (similarity score between a mouse model and a human disease described by <a href="#">Smedley et al 2013</a> )

# Steps 2, 3, 4: Aggregating data

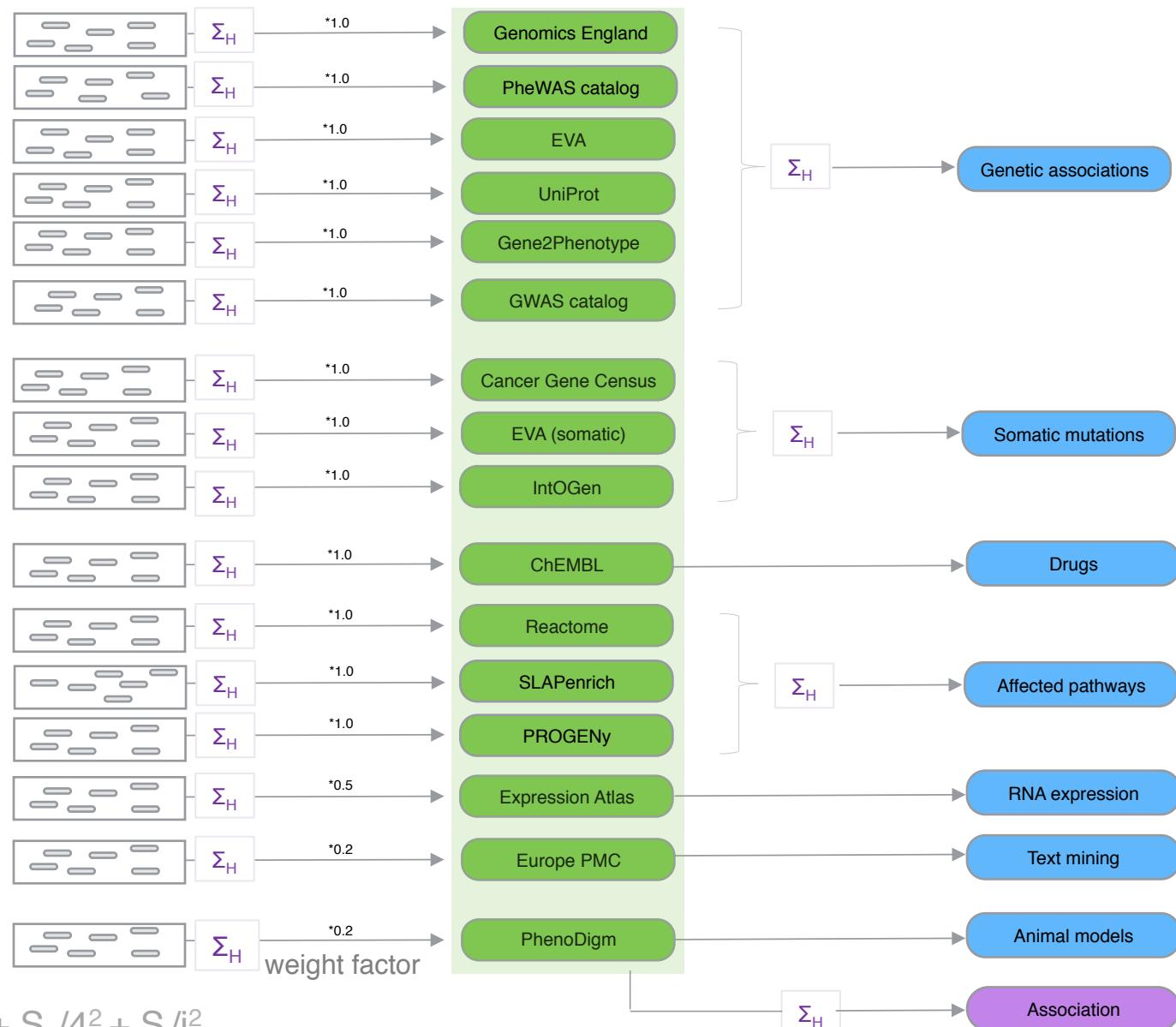
Score: 0 to 1 (max)

Calculated at four levels:

- Evidence
- Data source
- Data type
- Overall

Aggregation with  $\Sigma_H$   
(harmonic sum)

Note: Each data set has its own scoring and ranking scheme



$$\Sigma_H = S_1 + S_2/2^2 + S_3/3^2 + S_4/4^2 + \dots + S_i/i^2$$

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# Demo 1: Disease centric workflow

Which targets are associated with a disease?



What is the evidence for the association between a target and a disease?



Find new targets for drug discovery

multiple sclero 🔍

**multiple sclerosis**  
2697 targets associated

💡 Disease  
An autoimmune disorder mainly affecting young adults and characterized by destruction of myelin in the central nervous system. Pathologic findings include multiple sharply demarcated areas of demyelination throughout the white matter of the central nervous system. Clinical manifestations include vis...

Targets  
MBP myelin basic protein

Diseases  
relapsing-remitting **multiple sclerosis**  
autoimmune disease > multiple sclerosis > relapsing-remitting multiple ...

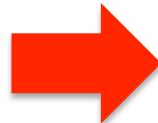
Pages 7 - 15

<https://www.targetvalidation.org/>



# Demo 2: Annotations of targets/diseases

What can I find about a disease?



What is the information available for my target?

Target profile page

**CD86**

CD86 molecule

Synonyms: B7.2, B7-2, CD28LG2

Receptor involved in the costimulatory signal essential for T-lymphocyte proliferation and interleukin-2 production, by binding CD28 or CTLA-4. May play a critical role in the early events of T-cell a...

Disease profile page

**multiple sclerosis**

Synonyms: MS (Multiple Sclerosis), MS, Multiple Sclerosis, Acute Fulminating, Disseminated Sclerosis, MULTIPLE...

Pages 16 - 25

<https://www.targetvalidation.org/>



# Demo 3: Target centric workflow

Which diseases are associated with a target?



Open Targets Platform

## CD86

CD86 molecule | [View associated diseases](#)

Receptor involved in the costimulatory signal essential for T-cell proliferation and activation. CD86 is also known as B7-2 and is expressed on activated T-cells, dendritic cells, and B cells.

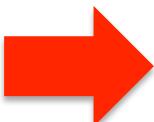
Open Targets Platform

### Find new targets for drug discovery

cd86

**CD86**  
CD86 molecule  
446 diseases associated  
Target

Receptor involved in the costimulatory signal essential for T-lymphocyte proliferation and interleukin-2 production, by binding CD28 or CTLA-4. May play a critical role in the early events of T-cell activation and costimulation of naive T-cells, such as deciding between immunity and anergy that is mediated by CD28 and CTLA-4 respectively.



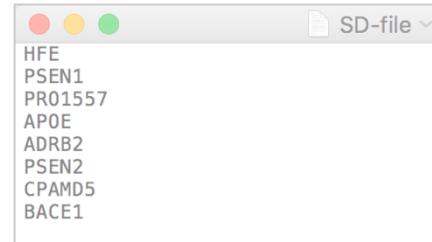


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# Hands-on exercises

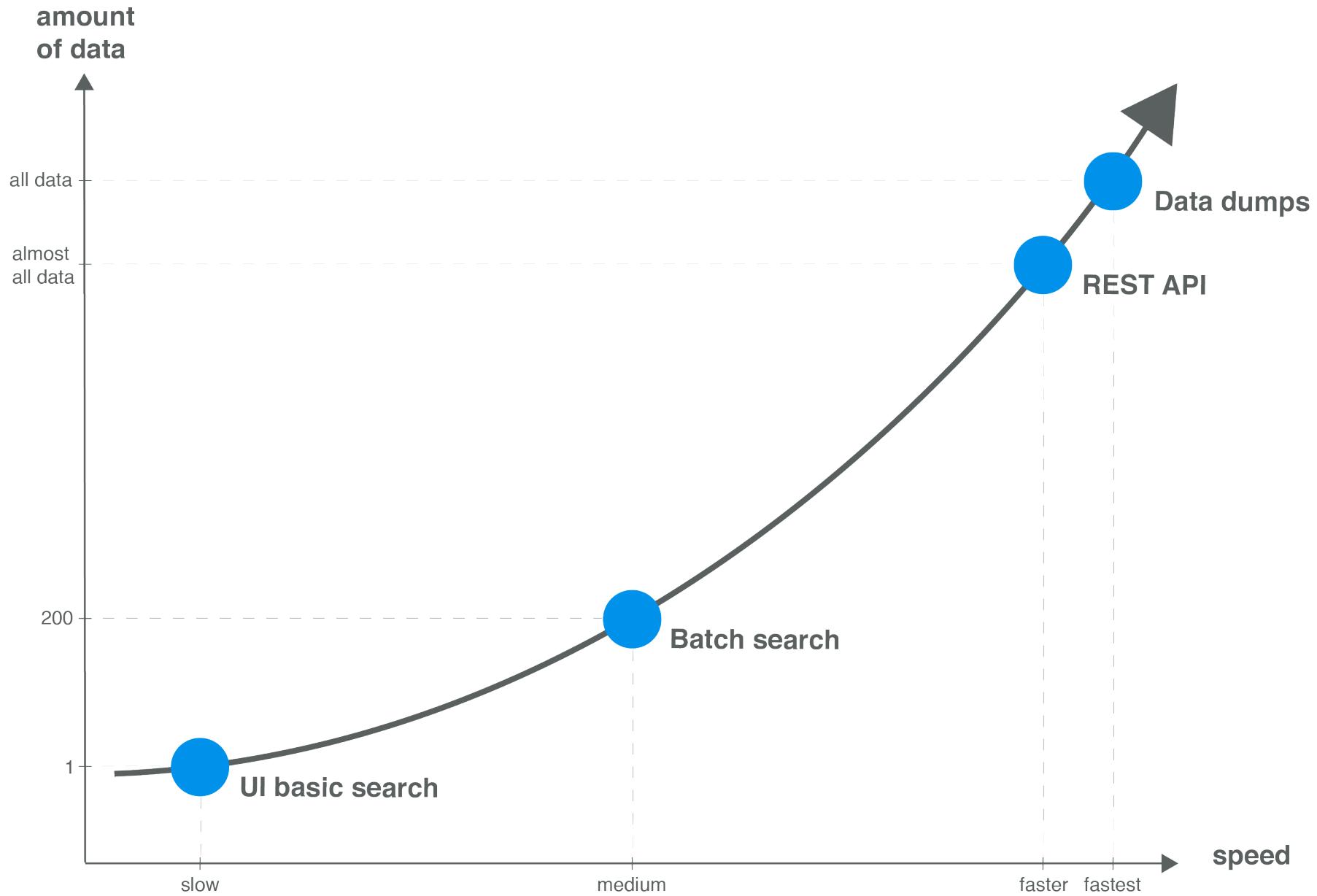
Pages 31-35



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- Feedback and wrap up

# Modes of access → data volume



# Demo 4: search of many targets at once



We have a list of 37 human genes that are potential targets for breast carcinoma

Are these targets also represented in other diseases?

Which pathways and GO terms are enriched in this set of genes?



# Programmatic access with REST-API

Server

Endpoint

Parameters

<https://api.opentargets.io/v3/platform/public/association/filter>

?target=ENSG00000163914&size=10000&fields=target.id&fields=disease.id

<https://api.opentargets.io/v3/platform/docs/swagger-ui>

# How to run our REST endpoints (option 1)

Paste the URL in the location bar of your browser

The screenshot shows a browser window with the following details:

- Address Bar:** Secure | <https://api.opentargets.io/v3/platform/public/association/filter?target=ENSG00000167207>
- Content Area:** A large JSON object representing the search results for the target gene ENSG00000167207. The JSON is too long to show in full here, but it includes fields like "from", "took", "next", "data\_version", "query", "target", "association\_score", and various association types (e.g., "genetic\_association", "somatic\_mutation", "known\_drug"). It also lists data sources and specific phenotypic associations.

```
{  
    from: 0,  
    took: 22,  
    ▼ next: [  
        1.3668802,  
        "ENSG00000167207-Orphanet_101988"  
    ],  
    data_version: "17.09",  
    ▼ query: {  
        ▼ sort: [  
            "harmonic-sum.overall"  
        ],  
        search: null,  
        rna_expression_level: 0,  
        protein_expression_tissue: [ ],  
        ▼ scorevalue_types: [  
            "overall"  
        ],  
        datatype: [ ],  
        fields: null,  
        format: "json",  
        facets_size: null,  
        disease: [ ],  
        protein_expression_level: 0,  
        datastructure: "default",  
        facets: "false",  
        rna_expression_tissue: [ ],  
        ▼ target: [  
            "ENSG00000167207"  
        ],  
        target_class: [ ],  
        cap_scores: true,  
        pathway: [ ],  
        size: 10  
    }  
}
```



JSONView

# How to run our REST endpoints (option 2)

Command line e.g. CURL -X GET

```
denise-ml:~ denise$ curl -X GET https://api.opentargets.io/v3/platform/public/association/filter?target=ENSG00000167207&is_direct=true
[[1] 45611
[2] 45612
[2]+ Done
denise-ml:~ denise$ {"from": 0, "took": 13, "next": 1.3668802, "ENSG00000167207-Orphanet_101988": [{"target": {"id": "ENSG00000167207", "label": "nucleotide binding oligomerization domain containing 2"}, "association_score": {"datatypes": {"literature": 0.2974496, "slapenrich": 0.0, "expression_atlas": 0.0006625794025179989, "europemc": 0.14497512075102087, "reactome": 0.29744967878526557, "eva": 0.9245864351309815, "gene2phenotype": 0.0, "gwas_catalog": 1, "intogen": 0.0, "gene_census": 0.0, "uniprot_somatic": 0.0, "eva_somatic": 0.0, "phewas_catalog": 0.0016}, "labels": [], "codes": []}, "path": [{"EFO_0000540"}], "label": "immune system disease"}, "id": "EFO_0000540", "literature": 1463.0, "rna_expression": 32.0, "genetic_association": 133.0, "somatic_mutation": 0.0, "known_drug": 0.0, "animal_model": 0.0, "total": 1820.0, "datasources": {"slapenrich": 0.0, "expression_atlas": 32.0, "europemc": 1463.0, "twentythousand": 2.0, "eva": 11.0, "gene2phenotype": 0.0, "gwas_catalog": 17.0, "intogen": 0.0, "genomics_england": 0.0, "reactome": 0.0, "uniprot_somatic": 0.0, "eva_somatic": 0.0, "phewas_catalog": 9.0}}, "id": "ENSG00000167207", "label": "nucleotide binding oligomerization domain containing 2"}, "id": "ENSG00000167207"}, "association_score": {"datatypes": {"literature": 0.0, "genetic_association": 1.0, "somatic_mutation": 0.0, "known_drug": 0.0, "animal_model": 0.0, "datasources": {"slapenrich": 0.0, "expression_atlas": 0.0, "europemc": 0.09408949039475947, "twentythousand": 1591672500813, "eva": 0.900426255952381, "gene2phenotype": 0.0, "gwas_catalog": 0.0, "intogen": 0.0, "gene_census": 0.0, "reactome": 0.0, "uniprot_somatic": 0.0, "eva_somatic": 0.0, "phewas_catalog": 0.00139053}}, "codes": [], "path": [{"EFO_0000508"}], "label": "genetic disorder"}, "id": "EFO_0000508"}, "is_direct": true}
```



# How to run our REST endpoints (option 3)

## Use our free Python client\*



The screenshot shows a documentation page for the opentargets Python client. The left sidebar has a blue header with the 'opentargets' logo and 'latest' version. It includes links for 'Search docs', 'Tutorial', 'High Level API', 'Low Level API', 'Code Documentation', and 'Changelog'. The main content area has a white header with 'Docs' and the URL 'opentargets - Python client for targetvalidation.org'. A purple circular icon is in the top right. The main title is 'opentargets - Python client for targetvalidation.org'. Below it, a paragraph states: 'opentargets is the official python client for the Open Targets REST API at targetvalidation.org'.

Advantage: you can change the way the associations are scored e.g. increase the weight given to text mining data

\* <http://opentargets.readthedocs.io/en/stable/index.html>

# User interface or REST-API?

- Scale and volume of your search or results
- Flexibility in the search
- Visualisation of the results



```
        ],
    },
- target: {
    id: "ENSG00000146648",
- gene_info: {
        symbol: "EGFR",
        name: "epidermal growth factor receptor",
        geneid: "ENSG00000146648"
    },
    target_type: "protein_evidence",
    activity: "gain_of_function"
},
validated_against_schema_version: "1.2.8",
sourceID: "reactome",
- loci: {
    - 7: {
        gene_end: 55211628,
        gene_begin: 55019021
    }
}
```

# Demo 5: REST API on a browser

Search for disease  
e.g. Alzheimer's

Find out how many targets  
have direct associations

Get the data source  
association scores for  
AD-APP

Get the evidence score for a  
APP–ADD



# REST API calls: some examples\*

GET

/public/search

<https://api.opentargets.io/v3/platform/public/search?q=alzheimer%27s>

GET

/public/association/filter

<https://api.opentargets.io/v3/platform/public/association/filter?target=ENSG00000142192>

[https://api.opentargets.io/v3/platform/public/association/filter  
?target=ENSG00000142192&direct=true](https://api.opentargets.io/v3/platform/public/association/filter?target=ENSG00000142192&direct=true)

GET

/public/evidence/filter

[https://api.opentargets.io/v3/platform/public/evidence/filter?  
target=ENSG00000142192&disease=EFO\\_0000249&datasource=uniprot&direct=true](https://api.opentargets.io/v3/platform/public/evidence/filter?target=ENSG00000142192&disease=EFO_0000249&datasource=uniprot&direct=true)

# Open Targets REST API

<https://api.opentargets.io/v3/platform/docs/swagger-ui>

## filter Methods to filter the available evidence.

**GET**

[\*\*/platform/public/association/filter\*\*](#) Filter available associations

**POST**

[\*\*/platform/public/association/filter\*\*](#) Batch query available associations

**GET**

[\*\*/platform/public/evidence/filter\*\*](#) Filter available evidence

**POST**

[\*\*/platform/public/evidence/filter\*\*](#) Batch filter available evidence

Private: methods used by the UI to serve external data. Subject to change without notice

# REST API: webinar

YouTube GB

Search

## getAssociationFilter



674 diseases associated with PTEN  
View PTEN profile

Filter by

Data type

Therapeutic areas

http://api.opentargets.io/v3/platform/public/association/filter?

target=ENSG00000171862

&offset=28:56 / 40:43

```
{  
    "from": 0,  
    "took": 25,  
    "next": [  
        "ENSG00000171862-Orphanet_210548"  
    ],  
    "data_version": "17.12",  
    "therapeutic_areas": [-],  
    "query": {-},  
    "total": 674,  
    "data": [  
        {  
            "target": {  
                "gene_info": {  
                    "symbol": "PTEN",  
                    "name": "phosphatase and tensin homolog"  
                },  
                "id": "ENSG00000171862"  
            },  
            "association_score": {  
                "datatypes": {  
                    "literature": 0.3241324475302135,  
                    "rna_expression": 0,  
                    "genetic_association": 1,  
                    "somatic_mutation": 1,  
                    "known_drug": 0,  
                    "animal_model": 0,  
                    "affected_pathway": 1  
                },  
                "overall": 1,  
                "datasources": {  
                    "slapenrich": 0.817215326415924,  
                    "expression_atlas": 0,  
                    "europeme": 0.3241324475302135,  
                    "ccle": 0.3241324475302135  
                }  
            }  
        }  
    ]  
}
```

<https://youtu.be/KQbfhwpeEvc>

# Data downloads



Open Targets Platform

About ▾ Help ▾ API ▾ Downloads Blog

## Data Download

All data from targetvalidation.org is available for download as compressed JSON files.

We provide downloads of all associations between target and disease calculated by the platform, as well as all the evidence used in calculating each associations. These are the same objects returned by the corresponding [/public/associations](#) and [/public/evidence](#) API methods. Head to the [API documentation](#) for further details.

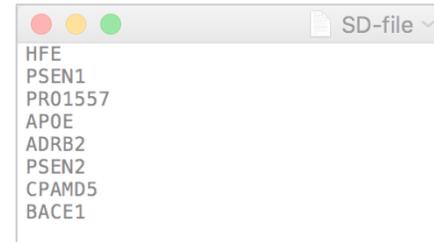
NOTE: the files below are useful only if you want to analyze the data. They are not a database dump and cannot be easily used to replicate the platform locally/somewhere else

2018 Aug

- [Association objects](#) (2018-06, 202MB)
- [Evidence objects](#) (2018-06, 2.44Gb)

# Hands-on exercises

Page 35



# Today: 10:00-16:00

- Introduction
- Open Targets Platform: live demos
- Exercises
- Other modes of data access
- Feedback survey and wrap up

Your feedback is important

<https://tinyurl.com/osong-181018>

# Open Targets Platform

- Resource of integrated multiomics data
- Added value (e.g. score) and links to original sources
- Graphical web interface: easy to use
- REST-API for larger, more flexible queries

21K  
targets

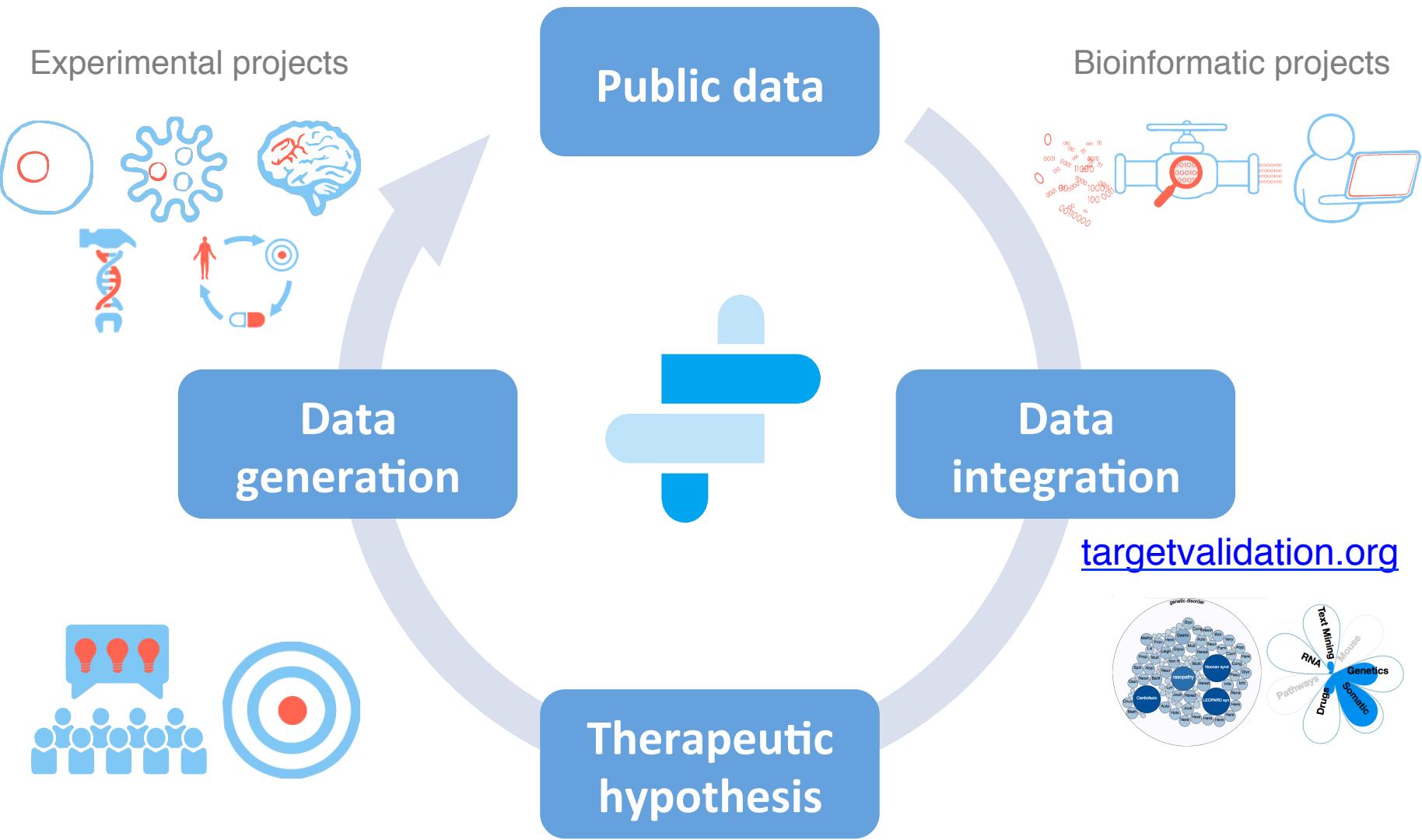
10K  
diseases

2.9 M  
associations

6.5 M  
evidence

August 2018 release

# Virtuous cycle in Open Targets



Concurrent  
[www.opentargets.org/projects](http://www.opentargets.org/projects)

# We support decision-making

Which targets are associated with a disease?

Can I find out about the mechanisms of the disease?

Are there FDA drugs for this association?



...

# Our breakthrough paper

Published online 8 December 2016

*Nucleic Acids Research*, 2017, Vol. 45, Database issue D985–D994  
doi: 10.1093/nar/gkw1055

## Open Targets: a platform for therapeutic target identification and validation

Gautier Koscielny<sup>1,2,\*</sup>, Peter An<sup>1,3</sup>, Denise Carvalho-Silva<sup>1,4</sup>, Jennifer A. Cham<sup>1,4</sup>, Luca Fumis<sup>1,4</sup>, Rippa Gasparyan<sup>1,3</sup>, Samiul Hasan<sup>1,2</sup>, Nikiforos Karamanis<sup>1,4</sup>, Michael Maguire<sup>1,4</sup>, Eliseo Papa<sup>1,3</sup>, Andrea Pierleoni<sup>1,4</sup>, Miguel Pignatelli<sup>1,4</sup>, Theo Platt<sup>1,3</sup>, Francis Rowland<sup>1,4</sup>, Priyanka Wankar<sup>1,3</sup>, A. Patrícia Bento<sup>1,4</sup>, Tony Burdett<sup>1,4</sup>, Antonio Fabregat<sup>1,4</sup>, Simon Forbes<sup>1,5</sup>, Anna Gaulton<sup>1,4</sup>, Cristina Yenyxe Gonzalez<sup>1,4</sup>, Henning Hermjakob<sup>1,4,6</sup>, Anne Hersey<sup>1,4</sup>, Steven Jupe<sup>1,4</sup>, Şenay Kafkas<sup>1,4</sup>, Maria Keays<sup>1,4</sup>, Catherine Leroy<sup>1,4</sup>, Francisco-Javier Lopez<sup>1,4</sup>, Maria Paula Magarinos<sup>1,4</sup>, James Malone<sup>1,4</sup>, Johanna McEntyre<sup>1,4</sup>, Alfonso Munoz-Pomer Fuentes<sup>1,4</sup>, Claire O'Donovan<sup>1,4</sup>, Irene Papatheodorou<sup>1,4</sup>, Helen Parkinson<sup>1,4</sup>, Barbara Palka<sup>1,4</sup>, Justin Paschall<sup>1,4</sup>, Robert Petryszak<sup>1,4</sup>, Naruemon Pratanwanich<sup>1,4</sup>, Sirarat Sarntivijal<sup>1,4</sup>, Gary Saunders<sup>1,4</sup>, Konstantinos Sidiropoulos<sup>1,4</sup>, Thomas Smith<sup>1,4</sup>, Zbyslaw Sondka<sup>1,5</sup>, Oliver Stegle<sup>1,4</sup>, Y. Amy Tang<sup>1,4</sup>, Edward Turner<sup>1,4</sup>, Brendan Vaughan<sup>1,4</sup>, Olga Vrousou<sup>1,4</sup>, Xavier Watkins<sup>1,4</sup>, Maria-Jesus Martin<sup>1,4</sup>, Philippe Sanseau<sup>1,2</sup>, Jessica Vamathevan<sup>4</sup>, Ewan Birney<sup>1,4</sup>, Jeffrey Barrett<sup>1,4,5</sup> and Ian Dunham<sup>1,4,\*</sup>

<sup>1</sup>Open Targets, Wellcome Genome Campus, Hinxton, Cambridge, CB10 1SD, UK, <sup>2</sup>GSK, Medicines Research Center, Gunnels Wood Road, Stevenage, SG1 2NY, UK, <sup>3</sup>Biogen, Cambridge, MA 02142, USA, <sup>4</sup>European Bioinformatics Institute (EMBL-EBI), Wellcome Genome Campus, Hinxton, Cambridge, CB10 1SD, UK, <sup>5</sup>Wellcome Trust Sanger Institute, Wellcome Genome Campus, Hinxton, Cambridge, CB10 1SA, UK and <sup>6</sup>National Center for Protein Research, No. 38, Life Science Park Road, Changping District, 102206 Beijing, China

Received August 19, 2016; Revised October 19, 2016; Editorial Decision October 20, 2016; Accepted November 03, 2016

# Get in touch



<https://docs.targetvalidation.org/>



[support@targetvalidation.org](mailto:support@targetvalidation.org)



<https://tinyurl.com/opentargets-youtube>



[@targetvalidate](https://twitter.com/targetvalidate)



<http://tinyurl.com/opentargets-in>



[blog.opentargets.org/](https://blog.opentargets.org/)

# Acknowledgements



Open Targets

# Coming up

## Open Targets Genetics

Search for a gene, variant or trait...



Examples:

[PCSK9](#) [1\\_154426264\\_C\\_T](#) [rs4129267](#) [Crohn's disease \(de Lange KM et al. 2017\)](#)

[Subscribe to our newsletter](#)

- Tool to map variants to genes to traits
- GWAS, LD expansion, functional genomics
- Association → causation?



Open Targets

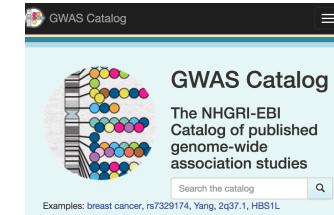
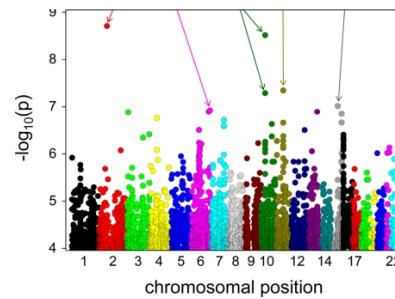
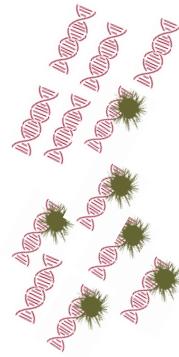
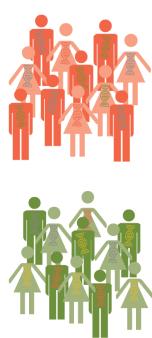
# Extra extra extra

Details on data sources to associate  
targets and diseases

Other Open Targets resources

# Data sources: GWAS catalog

- Genome Wide Association Studies
- Array-based chips → genotyping 100,000 SNPs genomewide



# Data sources: UniProt

- Protein: sequence, annotation, function



- Manual curation of coding variants in patients

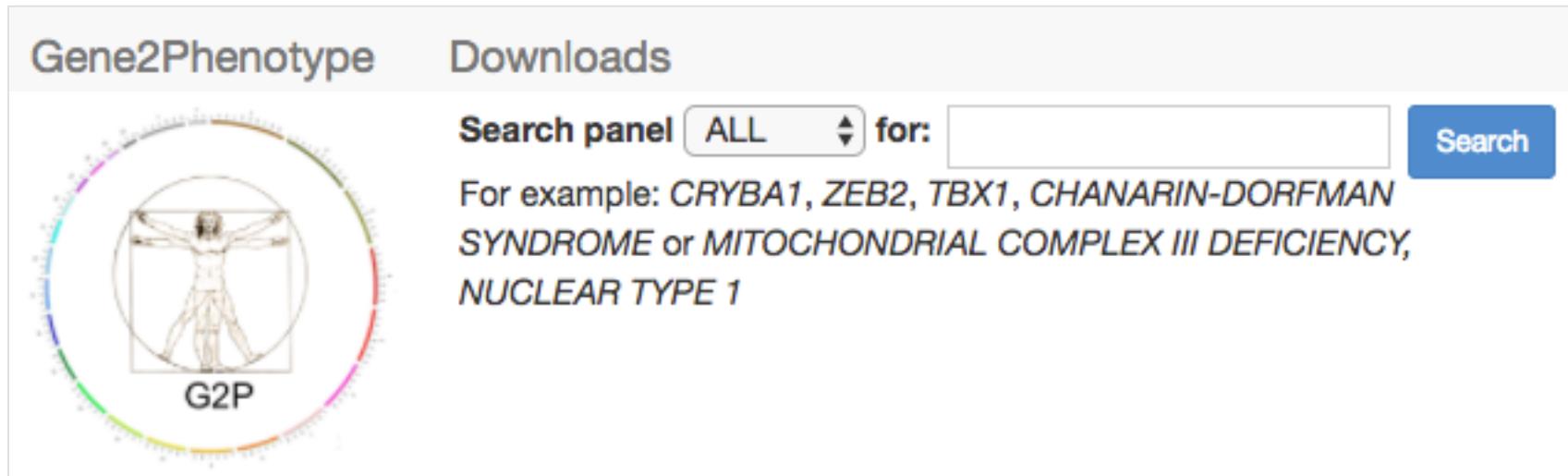


EMBL-EBI train online



Open Targets

# Data sources: Gene2Phenotype



Gene2Phenotype      Downloads

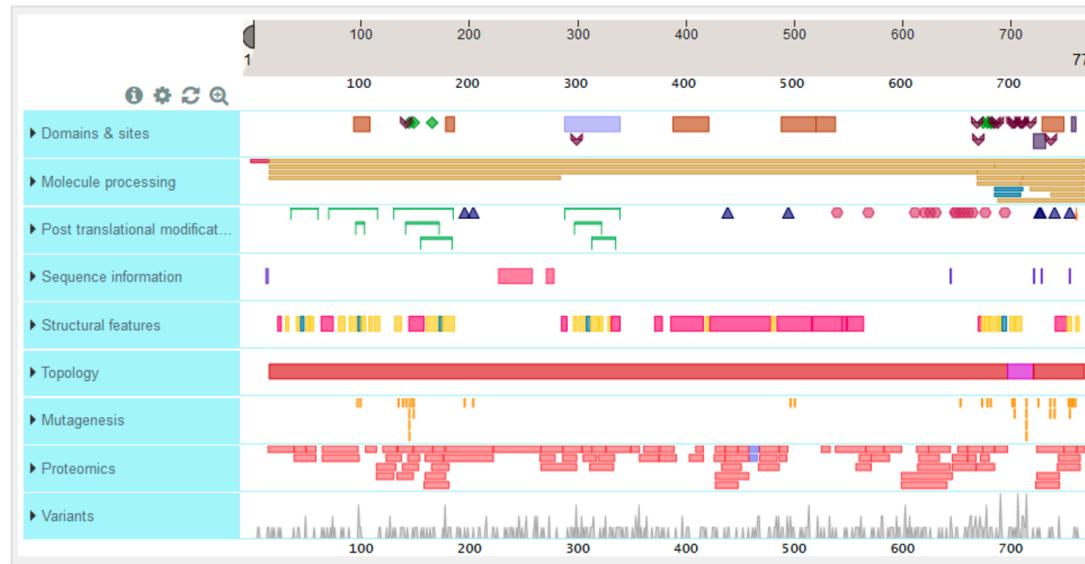
Search panel ALL for:  **Search**

For example: **CRYBA1, ZEB2, TBX1, CHANARIN-DORFMAN SYNDROME or MITOCHONDRIAL COMPLEX III DEFICIENCY, NUCLEAR TYPE 1**

- Variants, genes, phenotypes in rare diseases
- Literature curation → consultant clinical geneticists in the UK

# Data sources: UniProt

- Protein: sequence, annotation, function



- Manual curation of coding variants in patients



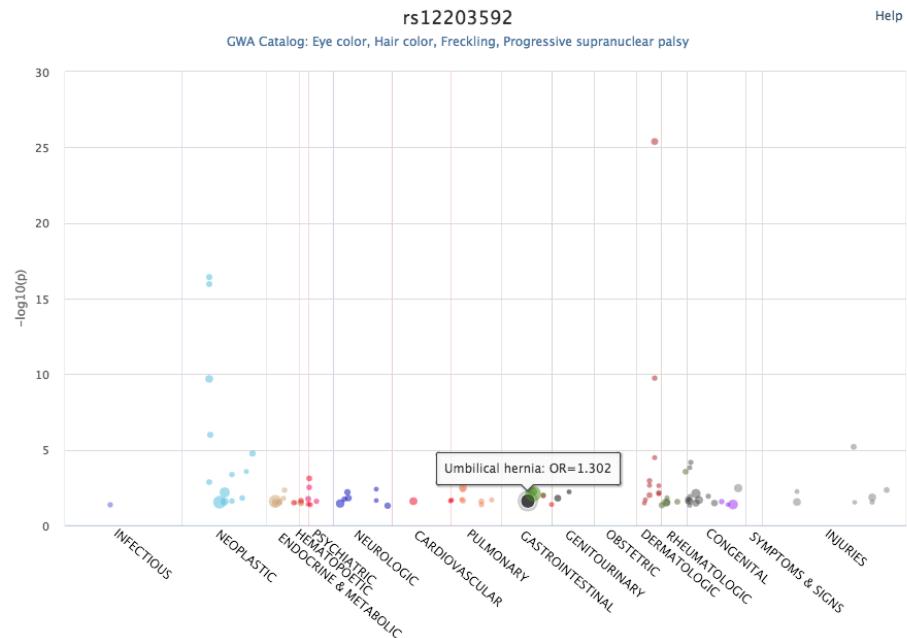
EMBL-EBI train online



Open Targets

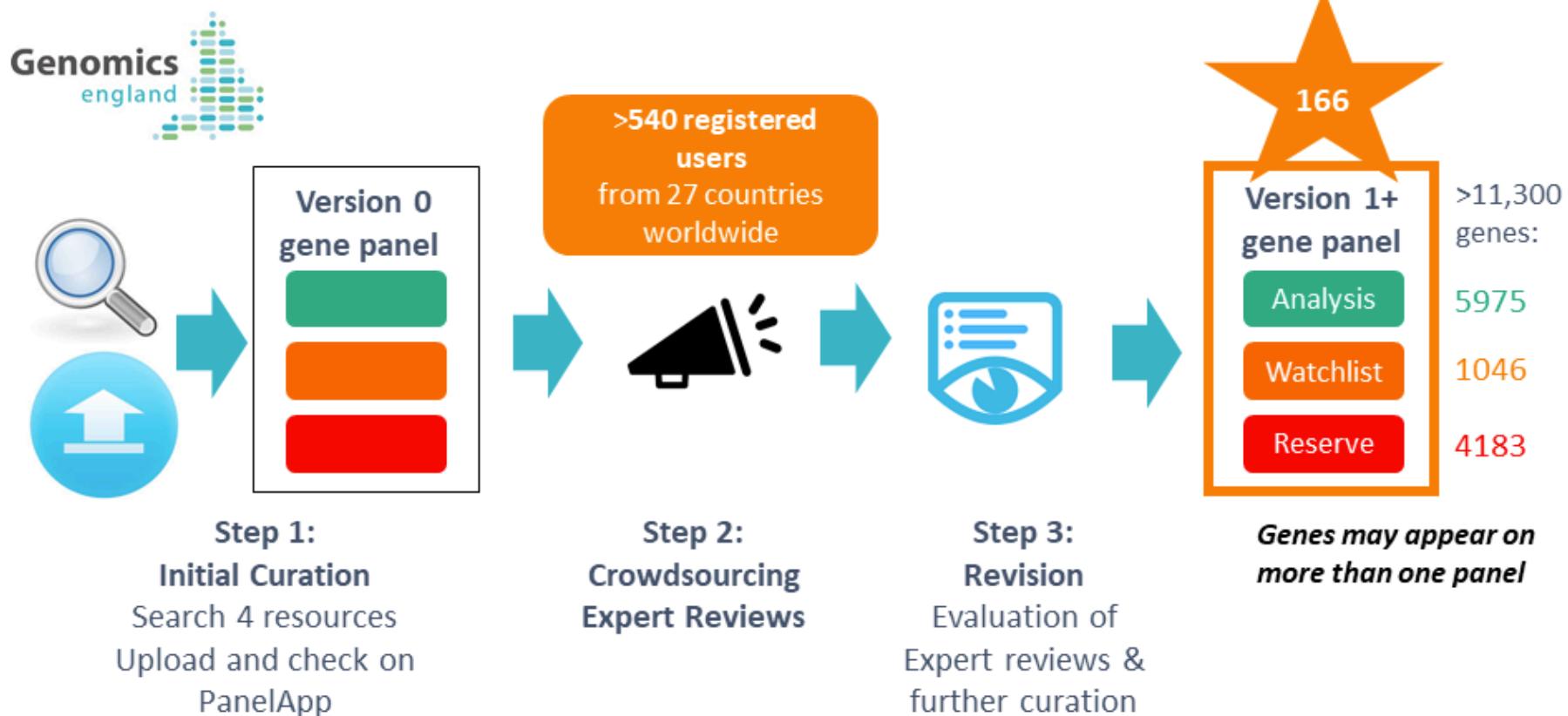
# Data sources: PheWAS

- Phenome Wide Association Studies
- A variant associated with multiple phenotypes
- Clinical phenotypes derived from EMR-linked biobank BioVU
- ICD9 codes mapped to EFO



# Data sources: GE PanelApp

- Aid clinical interpretation of genomes for the 100K project
- We include ‘green genes’ from version 1+ and phenotypes



Germline  
variants

Somatic  
mutations

# Data sources: EVA

- With ClinVar information for rare diseases
- Clinical significance: pathogenic, protective

The screenshot shows the European Variation Archive (EVA) Clinical Browser interface. The top navigation bar includes links for Home, Submit Data, Study Browser, Variant Browser, Clinical Browser (which is highlighted in dark blue), GA4GH, API, FAQ, and Feedback. Below the navigation is a search bar with a magnifying glass icon and a "Filter" button. To the right of the search bar is the title "ClinVar Browser" with an information icon. The main content area displays a table of ClinVar variants. The table has columns for Position, Affecte..., Most Severe Consequence..., Trait, Clinical Significance, and ClinVar ID. The first few rows show variants for the MSH6 gene on chromosome 2, with positions ranging from 480,000,000 to 490,000,000. The clinical significance for most variants is listed as Benign.

...	Posi...	Affecte... i	A...	Most Severe Consequence...	Trait	Clinical Significance	ClinVar ...
2	480...	MSH6	T/G	upstream_gen...	Lynch synd...	Benign	RCV000...
2	480...	MSH6	G/A	upstream_gen...	Lynch synd...	Benign	RCV000...
2	480...	MSH6	C/T	upstream_gen...	Lynch synd...	Benign	RCV000...
2	480...	MSH6	C/T	upstream_gen...	Lynch synd...	Benign	RCV000...
2	480...	MSH6	G/T	5_prime_UTR...	Lynch synd...	Uncertain s...	RCV000...
2	480...	MSH6	G/T	5_prime_UTR...	Hereditary ...	conflicting ...	RCV000...



# Data sources: The Cancer Gene Census

Census

Breakdown

Abbreviations

*The cancer Gene Census is an ongoing effort to catalogue those genes for which mutations have been causally implicated in cancer. The original census and analysis was published in [Nature Reviews Cancer](#) and supplemental analysis information related to the paper is also available.*

- Genes with mutations causally implicated in cancer
- Gene associated with a cancer plus other cancers associated with that gene

# Data sources: IntOGen

The screenshot shows the homepage of the intOGen website. At the top is a navigation bar with an orange gradient background. From left to right, it contains: the intOGen logo (a stylized orange 'i' icon followed by the word 'intOGen'), a 'Search' button with a magnifying glass icon, a 'Downloads' button with a download icon, an 'Analysis' button with a gear icon, an 'About' button with a speech bubble icon, and a 'Sign In' button with a user profile icon.

The main content area features the intOGen logo again, this time with the full name 'intOGen' in a large serif font next to a smaller orange 'i' icon. To the right of the name is the tagline 'Integrative Onco Genomics' in orange text.

- Genes and somatic (driver) mutations, 28 cancer types
- Involvement in cancer biology
- Rubio-Perez et al. 2015

# Data sources: ChEMBL

EMBL-EBI

# ChEMBL

EBI > Databases > Small Molecules > ChEMBL Database > Home

Search ChEMBL... Compounds Targets Assays

Ligand Search Target Search Browse Targets Browse Drugs Browse Drug Targets

- Known drugs linked to a disease and a known target
- FDA approved for clinical trials or marketing



EMBL-EBI train online



Open Targets

Affected  
pathways

# Data sources: Reactome



The image shows the Reactome homepage. At the top left, there is a purple box containing the text "Affected pathways". The main title "REACTOME" is displayed in large white letters, with "A CURATED PATHWAY DATABASE" in smaller text below it. To the right of the title is a decorative graphic featuring a red sphere, blue and green abstract shapes, and arrows. Below the title is a navigation bar with links: "About", "Content", "Documentation", "Tools", "Community", "Download", and "Contact". To the right of the navigation bar is a search bar containing the placeholder text "e.g. O95631, NTN1, signalin" and a "Search" button.

- Biochemical reactions and pathways
- Manual curation of pathways affected by mutations



EMBL-EBI train online



Open Targets

# Data sources: SLAPenrich

## METHOD

### Dissecting the genomic heterogeneity of cancer hallmarks' acquisition with SLAPenrich

Francesco Iorio<sup>1,5†</sup>, Luz Garcia-Alonso<sup>1,5</sup>, Jonathan Brammell<sup>2</sup>, Iñigo Martincorena<sup>2</sup>, David R Wille<sup>3,5</sup>, Ultan McDermott<sup>2,5</sup> and Julio Saez-Rodriguez<sup>1,4,5\*†</sup>

- 374 pathways curated and mapped to cancer hallmarks
- Divergence of the total number of cancer samples with genomic alterations
- Mutational burden and total exonic block length of genes

# Data sources: PROGENy

ARTICLE

DOI: 10.1038/s41467-017-02391-6

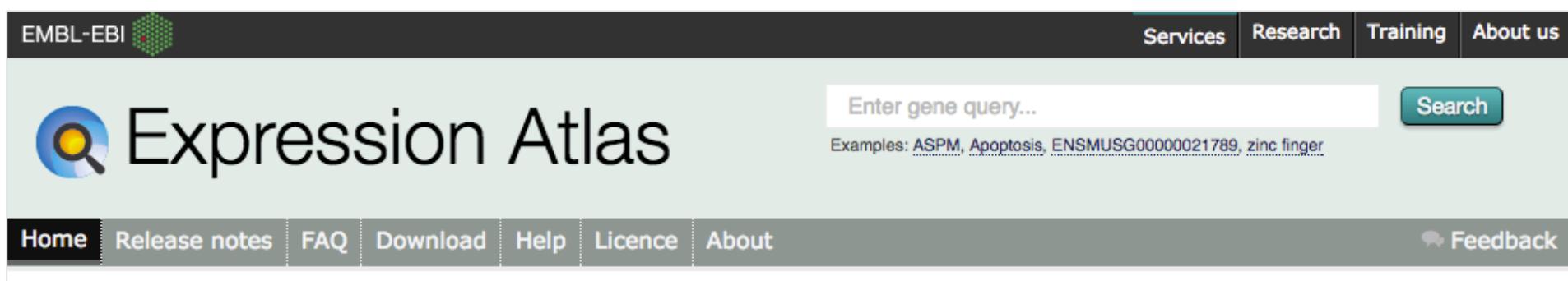
OPEN

## Perturbation-response genes reveal signaling footprints in cancer gene expression

Michael Schubert<sup>1</sup>, Bertram Klinger<sup>2,3</sup>, Martina Klünemann<sup>2,3</sup>, Anja Sieber<sup>2,3</sup>, Florian Uhlitz<sup>2,3</sup>, Sascha Sauer<sup>4</sup>, Mathew J. Garnett<sup>5</sup>, Nils Blüthgen<sup>2,3</sup> & Julio Saez-Rodriguez<sup>2,3</sup>

- Comparison of pathway activities between normal and primary samples from The Cancer Genome Atlas
- Inferred from RNA-seq: 9,250 tumour and 741 normal samples
- EGFR, hypoxia, JAK/STAT, MAPK, NFκB, PI3K, TGFb, TNF $\alpha$ , Trail, VEGF, and p53

# Data sources: Expression Atlas



The screenshot shows the Expression Atlas website. At the top, there's a dark header bar with the EMBL-EBI logo on the left and navigation links for Services, Research, Training, and About us on the right. Below the header is a search bar with a placeholder "Enter gene query..." and a "Search" button. To the left of the search bar is a magnifying glass icon. The main title "Expression Atlas" is prominently displayed in large black font next to the search bar. Below the title is a navigation bar with links for Home, Release notes, FAQ, Download, Help, Licence, and About. On the far right of this bar is a "Feedback" link with a speech bubble icon.

- Baseline expression for human genes
  - target profile page
- Differential mRNA expression (healthy *versus* diseased):
  - target-disease associations



EMBL-EBI train online



# Data sources: Europe PMC



Europe PMC

About

Tools

Developers

Help

Europe PMC plus

Search worldwide, life-sciences literature

- Mining titles, abstracts, full text in research articles
- Target and disease co-occurrence in the same sentence
- Dictionary (not NLP)



EMBL-EBI train online



Open Targets

# Data sources: PhenoDigm

The screenshot shows the homepage of the PhenoDigm website. At the top, there is a dark header bar with the Wellcome Trust Sanger Institute logo on the left. To the right of the logo is a blue navigation bar with the following links: "ABOUT" (with a dropdown arrow), "Who we are", "Careers", "Study", "Sex in Science", "Groups", and "Campus". On the far right of the blue bar is a magnifying glass icon representing a search function. Below the header, the main title "Welcome to PhenoDigm (PHENOtype comparisons for DIsease and Gene Models)" is displayed in large, bold, black font. Underneath the title, there is a horizontal menu bar with three items: "Diseases" (which is highlighted in blue), "Tissue phenotype associations", and "Secondary phenotypes".

## Welcome to PhenoDigm (PHENOtype comparisons for DIsease and Gene Models)

Diseases Tissue phenotype associations Secondary phenotypes

- Semantic approach to associate mouse models with diseases

# Aggregating scores across the data

- Using a mathematical function, the harmonic sum\*

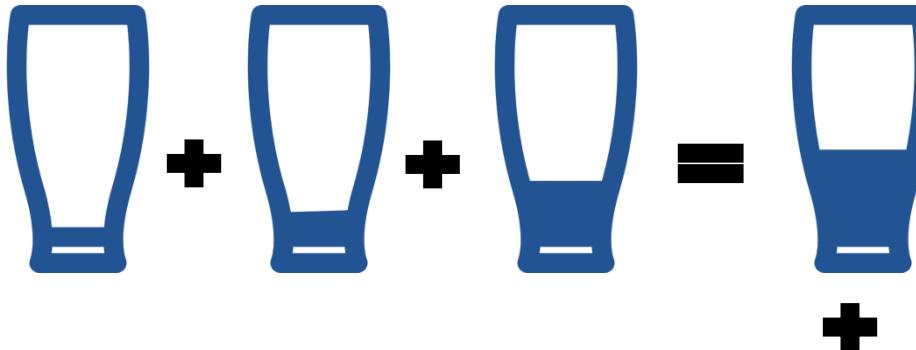
$$S_{1..i} = S_1 + \frac{S_2}{2^2} + \frac{S_3}{3^2} + \frac{S_4}{4^2} \dots + \frac{S_i}{i^2}$$

where  $S_1, S_2, \dots, S_i$  are the individual sorted evidence scores in descending order

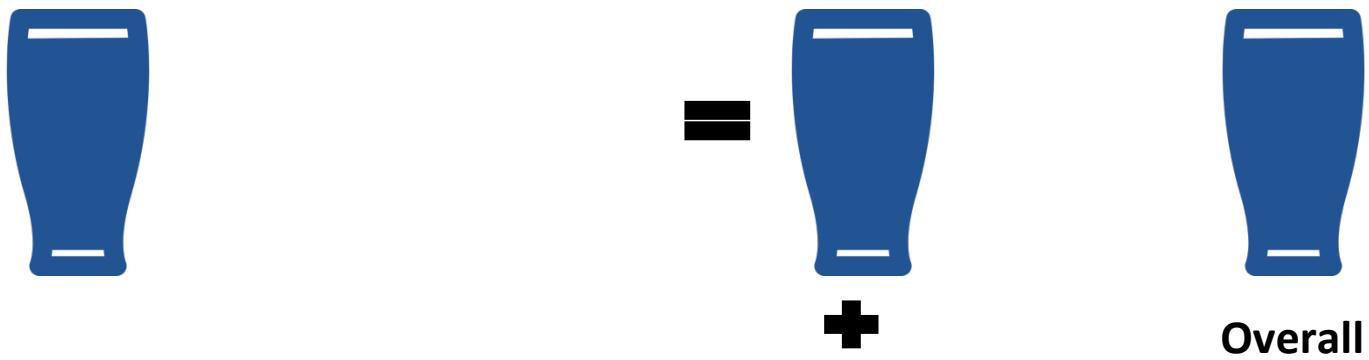
- Advantages:
  - A) account for replication
  - B) deflate the effect of large amounts of data e.g. text mining

# Target-Disease Association Score

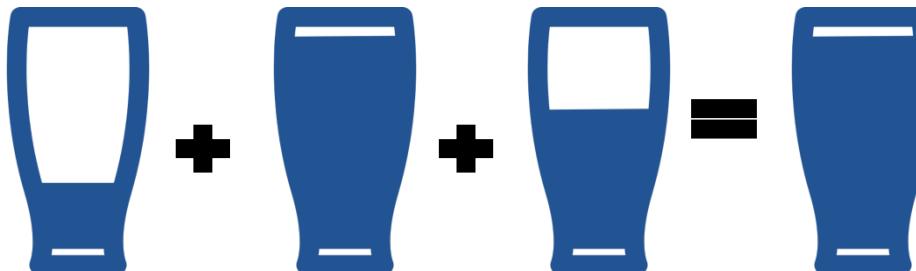
EuropePMC  
(Text Mining)



UniProt  
(Manual Curation)



ChEMBL  
(Manual Curation)



Overall

VERY simplified diagram

# How to search

Open Targets Platform

## Search results for pten

Found 32 results | 0.119 seconds

Refine by:

- Target 26
- Disease 6

PTEN  
Tumor suppressor, tyrosine-phosphatase, phosphatase and dual-specificity kinase, Target

GET /platform/public/search

```
{  
    from: 0,  
    took: 538,  
    data_version: "17.12",  
    - query: {  
        highlight: true,  
        fields: null,  
        datastructure: "default",  
        format: "json",  
        size: 675  
    },  
    total: 32, ←  
    - data: [  
        - {  
            - data: {  
                + ortholog: {...},  
                - top_associations: {  
                    - total: [  
                        - {  
                            score: 1,  
                            id: "ENSG00000171862-EFO_0000616"  
                        },  
                        - {  
                            score: 1,  
                            id: "ENSG00000171862-EFO_0000405"  
                        }  
                    ]  
                }  
            }  
        }  
    ]  
}
```

<https://api.opentargets.io/v3/platform/public/search?q=PTEN>

# How to get all diseases associated with a target

Open Targets Platform

About ▾ Help ▾ API ▾ Downloads Blog

674 diseases associated with PTEN

View PTEN profile

Filter by

Data type

Clear all × Select all ✓

- Genetic associations (50)
- Somatic mutations (187)
- Drugs (0)
- Affected pathways (49)
- RNA expression (19)
- Text mining (611)
- Animal models (0)

Therapeutic area

Bubbles Table Tree

Showing 1 to 50 of 674 entries

Search:

Disease	Association score	Genetic associations	Somatic mutations	Drugs
neoplasm				
cancer				
genetic disorder				
epithelial neoplasm				
carcinoma				
Inherited cancer-predisposing s...				
PTEN hamartoma tumor syndro...				
Overgrowth syndrome				

GET

[/platform/public/association/filter](#)

[http://api.opentargets.io/v3/platform/public/association/filter?](http://api.opentargets.io/v3/platform/public/association/filter?target=ENSG00000171862&direct=true)  
target=ENSG00000171862  
&direct=true

```
{  
    from: 0,  
    took: 25,  
    - next: [  
        1.4207987,  
        "ENSG00000171862-Orphanet_210548"  
    ],  
    data_version: "17.12",  
    + therapeutic_areas: [...],  
    + query: {...},  
    total: 674,  
    - data: [  
        - {  
            - target: {  
                - gene_info: {  
                    symbol: "PTEN",  
                    name: "phosphatase and tensin homolog"  
                },  
                id: "ENSG00000171862"  
            },  
            - association_score: {  
                - datatypes: {  
                    literature: 0.3241324475302135,  
                    rna_expression: 0,  
                    genetic_association: 1,  
                    somatic_mutation: 1,  
                    known_drug: 0,  
                    animal_model: 0,  
                    affected_pathway: 1  
                },  
                overall: 1,  
            - datasources: {  
                slapenrich: 0.817215326415924,  
                expression_atlas: 0,  
                europepmc: 0.3241324475302135,  
            }  
        }  
    ]  
}
```

# How to get the score for an association

674 diseases associated with PTEN

 View PTEN profile

Filter by

Data type

- Genetic associations (50) ▾
- Somatic mutations (187) ▾
- Drugs (0)
- Affected pathways (49) ▾
- RNA expression (19) ▾
- Text mining (611) ▾
- Animal models (0)

Therapeutic area

Bubbles Table Tree

Showing 1 to 50 of 674 entries

Search:



GET

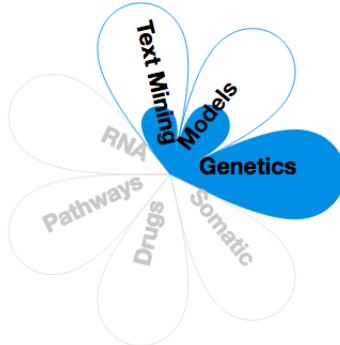
/platform/public/association

http://api.opentargets.io/v3/platform/  
public/association?id=ENSG00000171862  
-EFO\_0000616

```
{  
    from: 0,  
    took: 0,  
    data_version: "17.12",  
    query: { },  
    total: 1,  
    - data: [  
        - {  
            - target: {  
                - gene_info: {  
                    symbol: "PTEN",  
                    name: "phosphatase and tu-  
                    geneid: "ENSG00000171862"  
                },  
                id: "ENSG00000171862"  
            },  
            - association_score: {  
                - datatypes: {  
                    literature: 0.3241324475:  
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                    affected_pathway: 1  
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            }  
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    ]  
}
```

# How to get the evidence for an association

Evidence for DMD in Duchenne muscular dystrophy



Genetic associations

Table Browser

Rare diseases

Source: UniProt European Variation

Showing 1 to 10 of 297 entries

Search:

GET

[/platform/public/evidence/filter](http://api.opentargets.io/v3/platform/public/evidence/filter)

**DMD**  
dystrophin  
Synonyms: BMD, DDX142, DDX164, DDX206, DDX230, DDX239, DDX268, DDX269, DDX270, DDX272

Anchors the extracellular matrix to the cytoskeleton via F-actin. Ligand for dystroglycan. Component of the dystrophin-associated glycoprotein complex which accumulates at the neuromuscular junction (...)

**Duchenne muscular dystrophy**  
Synonyms: Severe dystrophinopathy, Duchenne type, DMD

```
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        - description: "Severe dystrophinopathy, Duchenne type, DMD",  
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        - variants: [{"id": "rs123456789", "chromosome": "X", "start": 123456789, "end": 123456789}],  
        - publications: [{"pmid": "123456789", "title": "The molecular pathology of Duchenne muscular dystrophy", "journal": "Nature"}, {"pmid": "123456789", "title": "The genetic basis of Duchenne muscular dystrophy", "journal": "Science"}]  
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    }  
  ]  
]
```

[http://api.opentargets.io/v3/platform/public/evidence/filter?  
target=ENSG00000198947&disease=Orphanet\\_98896&datatype=genetic\\_association](http://api.opentargets.io/v3/platform/public/evidence/filter?target=ENSG00000198947&disease=Orphanet_98896&datatype=genetic_association)