

INTUITION Tutorial for BioGateway

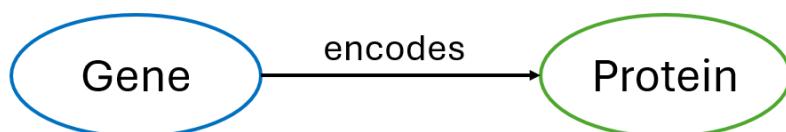
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1. Introduction

INTUITION (<https://semantics.inf.um.es/intuition/>) is a web application for user-friendly SPARQL query building. In this way, users can exploit RDF knowledge graphs without knowledge in SPARQL query language.

INTUITION analyses the knowledge network of an accessible endpoint, in this case, the current instance of BioGateway (<https://semantics.inf.um.es/biogateway>), and allows building biological queries graphically by defining search patterns: biological entities (nodes) that can be specified in detail through variables and are related through properties (edges).

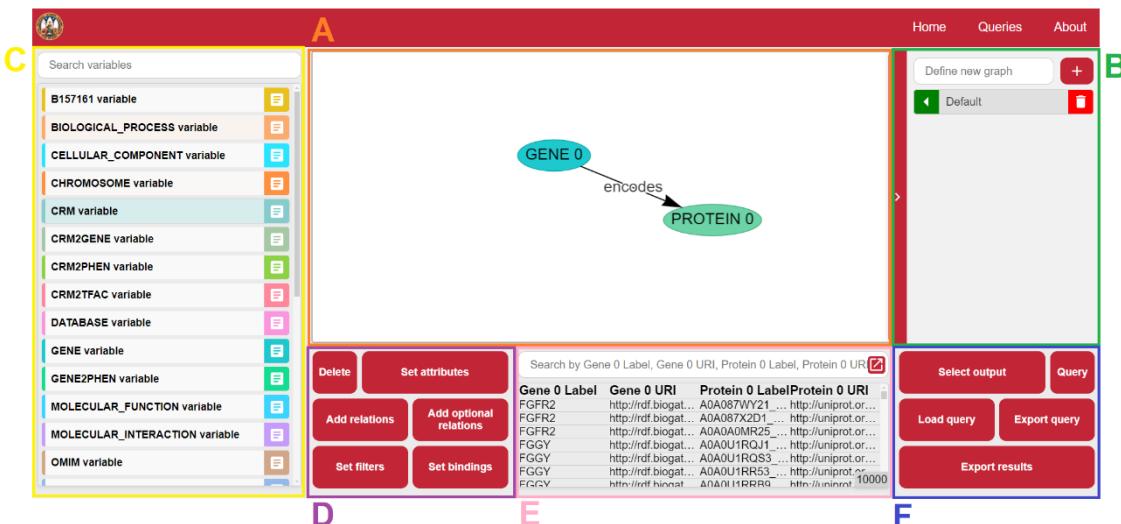
In a graph, nodes represent different types of biological entities, such as genes, proteins or CRMs, and edges (or properties) are used to specify different types of relations that exist between two nodes (for example, <Gene> <encodes> <Protein>). Some properties are also used to add attributes to entities.



2. Design

In INTUITION we distinguish different sections:

- A- Query building canvas.
- B- Union builder (Used for queries that use union clauses).
- C- Variable browser (Main types of entities in the network).
- D- Pattern designer (nodes and links):
 - Set attributes: Allows a user to edit the intrinsic properties of a variable, that distinguish one entity from another. For example, the name or description of a gene. Therefore, its inclusion acts as a filter because it permits to specify the entity or entities with a certain pattern of characteristics.
 - Add relations: Allows a user to include relations between entities to build queries of greater biological relevance. The inclusion of relations implies the insertion of a search pattern, so its use also selects/filters the knowledge network.
 - Add optional relations: Allows a user to include optional relations between entities. Their use does not act as a filter, but adds information when the pattern is met.
 - Set bindings: Enables the creation of custom variables using attributes included in the search pattern, renamed, or selected for inclusion in the output.
 - Set filters. Button to specify filters on attributes used in the search pattern, renamed, or selected to be included in the output. It can also be used to apply filters on new variables (bindings).
- E- Output display.
- F- Query builder:
 - Select output: output selector. Allow to indicate which variables are shown in the output screen.
 - Query: runs the query.
 - Load query: to load a previously designed query.
 - Export query: export the designed query.
 - Export results: exports the query results.

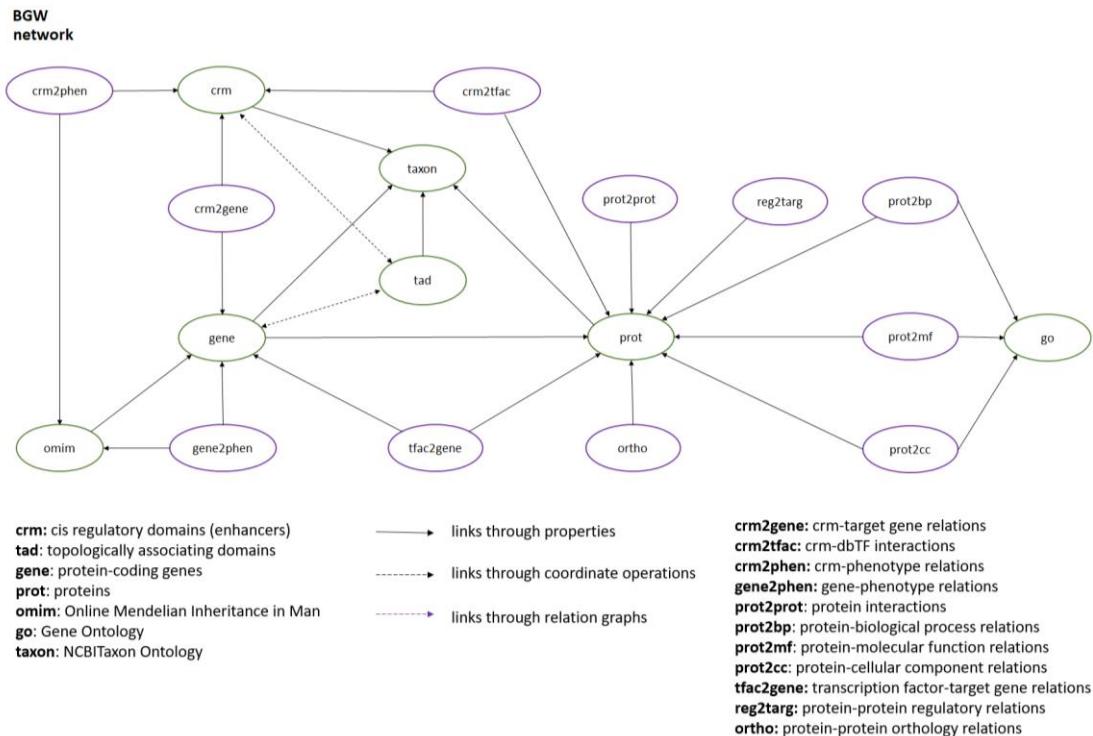


3. Variables and properties

Variables correspond to biological entities that we can use to develop query patterns. We can group these variables into 3 groups:

- 1- Variables corresponding to biological entities modelled by BioGateway:
 - Gene variable: protein-coding genes.
 - Protein variable: proteins.
 - CRM variable: cis-regulatory module (currently only enhancers).
 - TAD variable: topologically associated domain.
 - Database variable: databases.
 - Chromosome variable: chromosomes.
 - Reference_genome variable: genome assembly.
 - Transcription factor variable: transcription factors (currently only proteins that interact with CRM).
- 2- Variables corresponding to biological entities imported from external ontologies:
 - OMIM variable: entities from OMIM ontology (mainly phenotypes).
 - Molecular_interaction: entities from Molecular Interactions ontology (MI).
 - Cellular_component variable: cellular components from Gene Ontology (GO).
 - Molecular_function variable: molecular functions from GO.
 - Biological_process variable: biological processes from GO.
 - Root variable: top hierarchically class of NCBI Taxon Ontology.
 - Taxonomic_rank variable: top hierarchically class of NCBI Taxon Ontology.
- 3- Variables, modelled by BioGateway, corresponding to relations between biological entities:
 - crm2gene variable: relation between CRM and gene.
 - crm2phen variable: relation between CRM and phenotype.
 - crm2tfac variable: relation between CRM and protein (transcription factor).
 - gene2phen variable: relation between gene and phenotype.
 - tfac2gene variable: relation between gene and protein.
 - prot2prot: molecular interaction relation between proteins.
 - reg2targ variable: regulatory relation between proteins.
 - Ortho variable: orthology relation between proteins.
 - prot2cc variable: relation between protein and its cellular components.
 - prot2mf: relation between protein and its molecular functions.
 - prot2bp variable: relation between protein and its biological processes.

Properties are used to semantically relate different biological entities, and to provide attributes to these entities. These entities are detailed with examples and their domains [here](#). It also includes information about the vocabularies used.



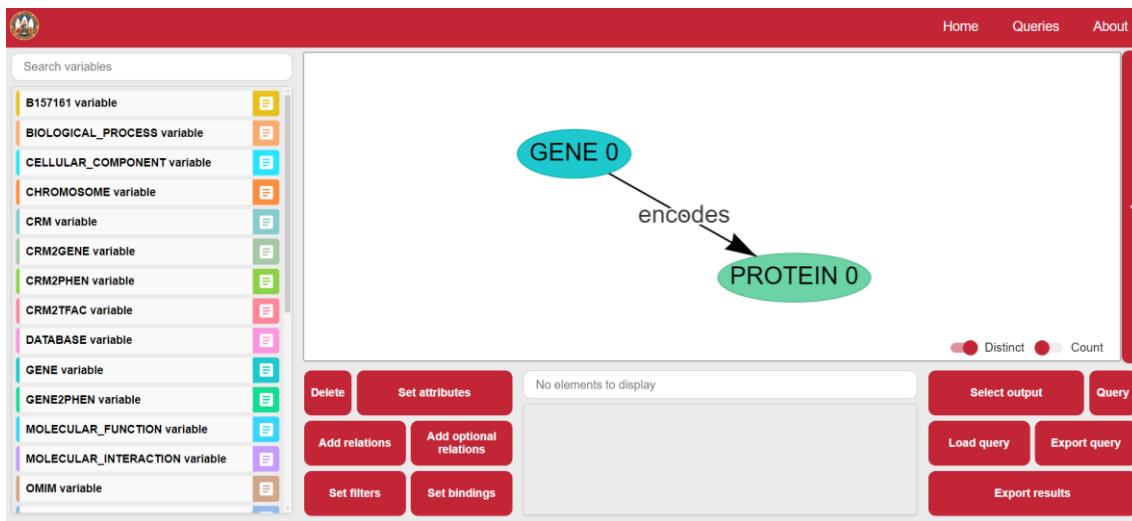
4. How to build a query in 6 steps

The query building process involves linking entities (nodes) with their attributes and/or other entities through properties (edges). We take as an example the previous case, the query: *Which proteins do the different genes encode?* (<Gene> <encodes> <Protein>).

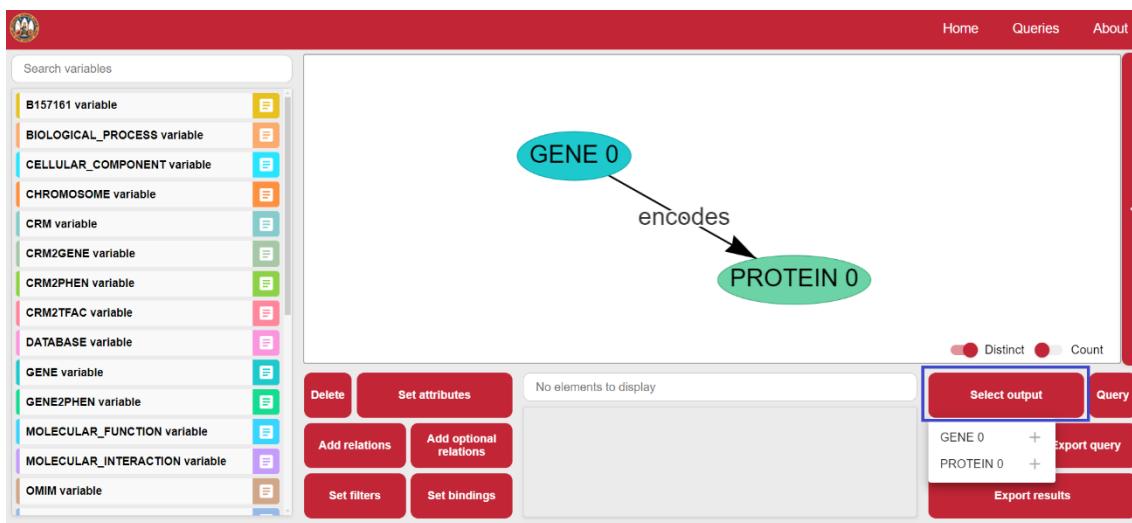
1. Select the first entity (subject node), in this case, “Gene”, in the “Variable browser”.

2. In “Add relations”, select the type of relation you want to use. In this case, “encodes”.

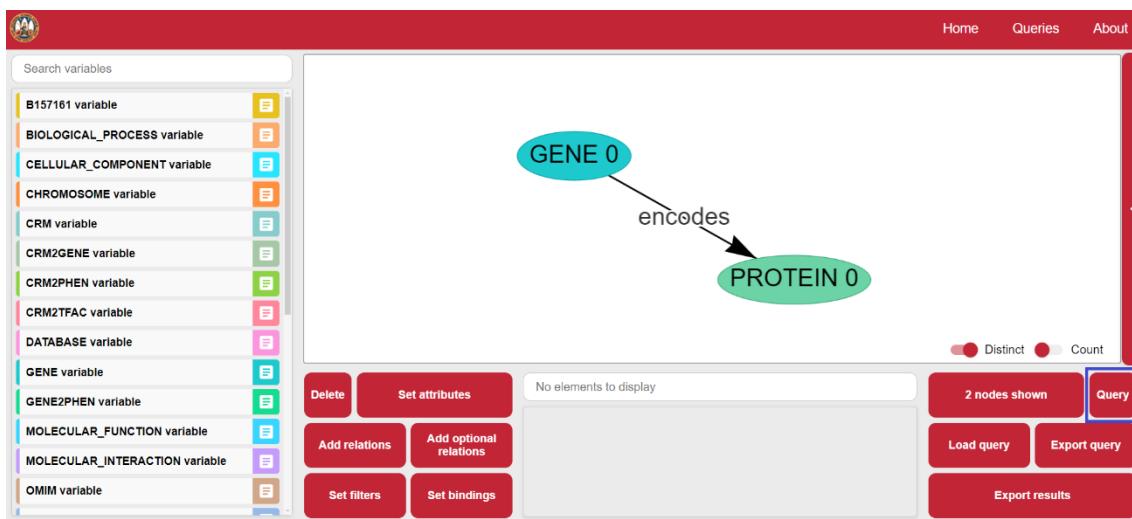
3. Select the second entity (object node). In this case, "Protein".



4. Select in "Select output" the data you want to show in the output (click on "+").



5. Click on "Query" to launch the query.



6. The results are available in the "Output display". Click on "Export results" to download the data. Click on "Export query" to save the query (json file).

Gene 0 Label	Gene 0 URI	Protein 0 Label	Protein 0 URI
FGR2	http://rdf.biogrid...	A0A087WY21...	http://uniprot.or...
FGR2	http://rdf.biogrid...	A0A0AMR25...	http://uniprot.or...
FGR2	http://rdf.biogrid...	A0A0U1RQJ1...	http://uniprot.or...
FGGY	http://rdf.biogrid...	A0A0U1RQS3...	http://uniprot.or...
FGGY	http://rdf.biogrid...	A0A0U1RR53...	http://uniprot.or...
FGGY	http://rdf.biogrid...	A0A0U1RRR9...	http://uniprot.or...

The generated SPARQL query can also be found by accessing the Console.

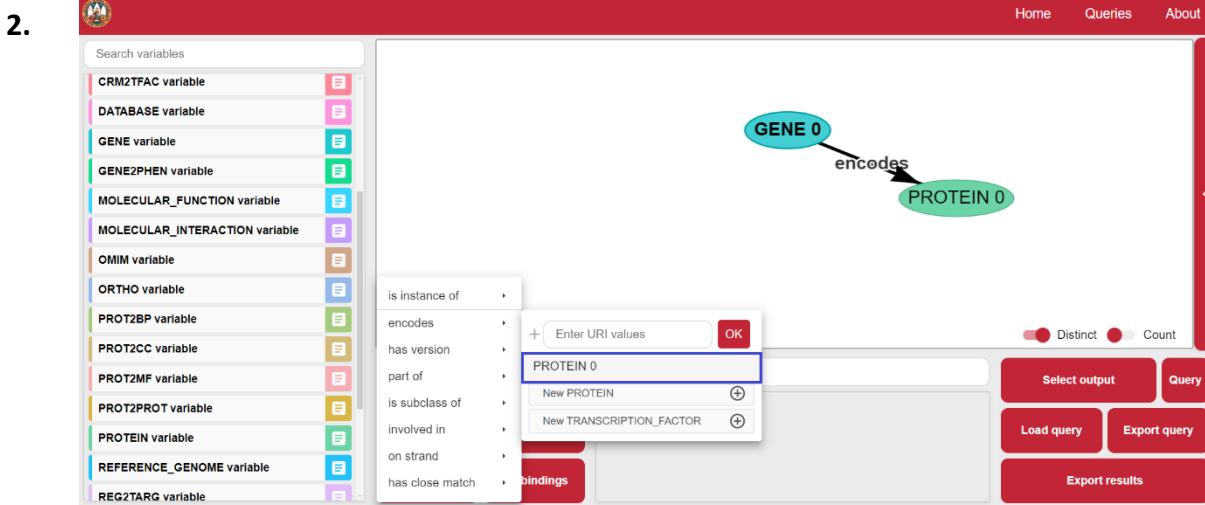
```

SELECT DISTINCT ?gene_0_URI ?protein_0_URI
WHERE {
  ?gene_0_URI <http://www.w3.org/2000/01/rdf-schema#subClassOf> <http://semanticscience.org/resource/SIO_010035> .
  ?gene_0_URI <http://semanticscience.org/resource/SIO_010070> ?protein_0_URI .
  ?protein_0_URI <http://www.w3.org/2000/01/rdf-schema#subClassOf> <http://semanticscience.org/resource/SIO_010043> .
}

```

Note: Links between entities can also be established by first introducing the two nodes of interest and then the relation between them. Following the previous example:

No elements to display	
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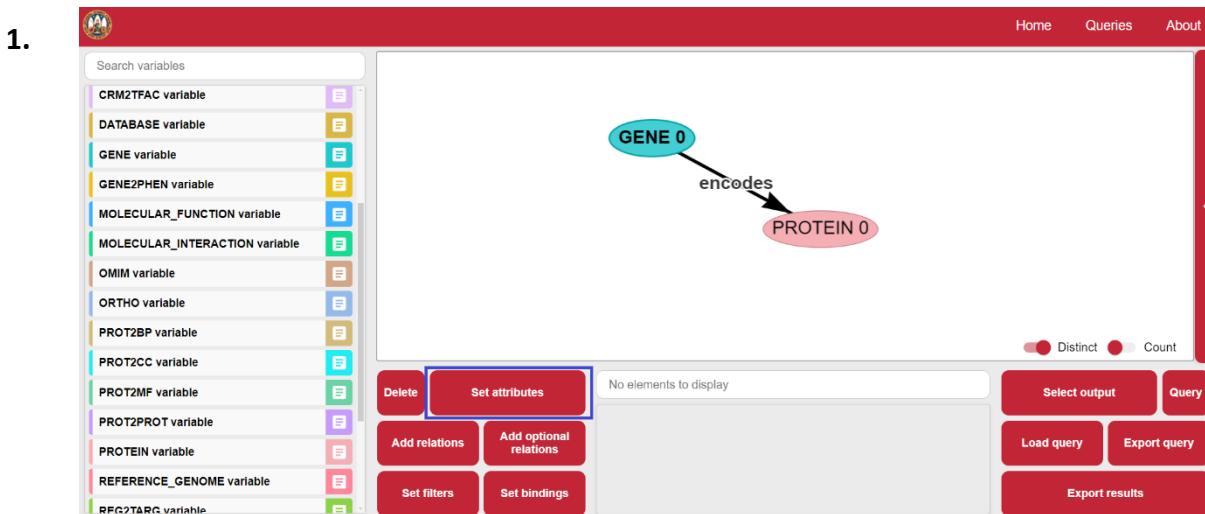


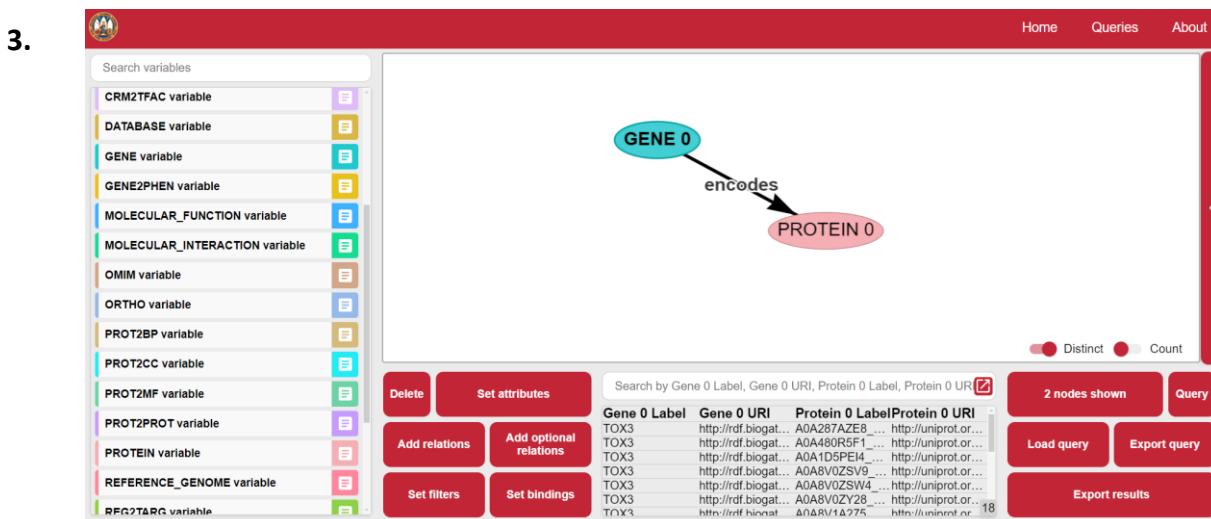
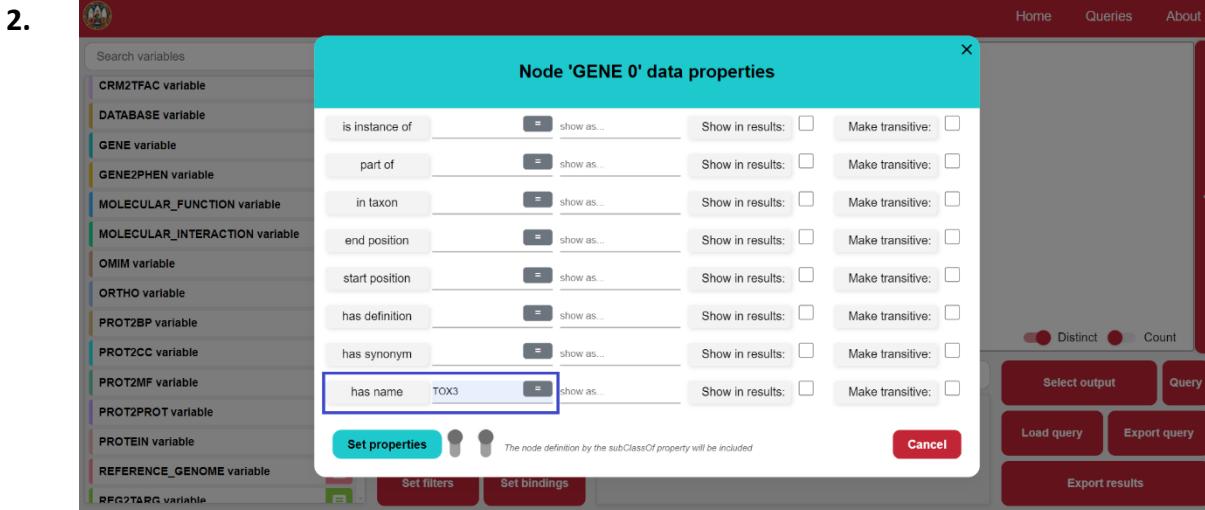
5. Data filtering and other possible operations

5.1. Filtering entities by their relations and attributes

Linking two biological entities (or variables) by their relation (properties) is the simplest way to create a search pattern. A search pattern selects the desired information from the knowledge network. However, any biological entity can also be selected by its characteristics or attributes.

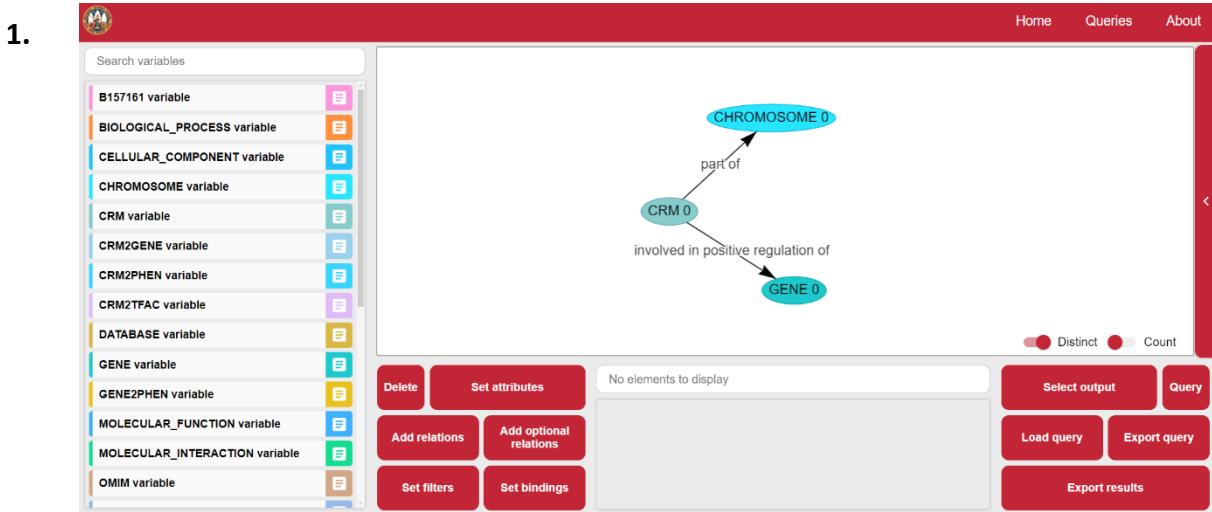
For example, genes can be selected by their names. Below we illustrate a use case that extends the previous query to: *Which proteins are encoded by the TOX3 gene?* To do this, we include the name of the gene in the attributes of the 'Gene' node (click on the corresponding node and then on the 'Set attributes' button).





By defining the desired characteristics of biological entities (by clicking on "Set attributes") we can select entities based on these characteristics (attributes). If the character is defined as "string" composed of letters and/or numbers we can use the operator '=' to find only exact strings, or the operator ' \subseteq ' to find substrings contained in a larger string. If the character is only numeric, we can find results equal to, larger, or smaller than, using the operators '=', '>', ' \geq ', '<', ' \leq '. To change the operators just click on the default operator.

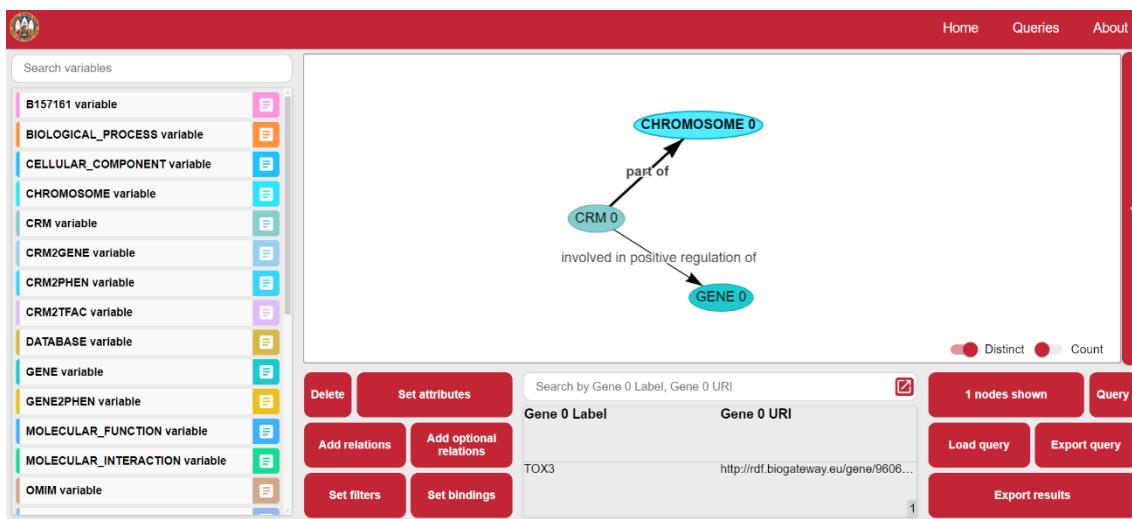
For example, we can query: *Which genes are regulated by enhancers that overlap with the chr16:52565276 mutation?* i.e. CRM sequences that positively regulate gene expression. To do this, we create the relations: <CRM> <part of> <Chromosome>, and <CRM> <involved in positive regulation of> <Gene>. Then we add attributes to the Chromosome (chromosome name) and CRM (sequence coordinates) nodes. Then we select the data output (Genes) and run the query.



2.

3.

4.



Variables can also be filtered clicking on “Set filters” button.

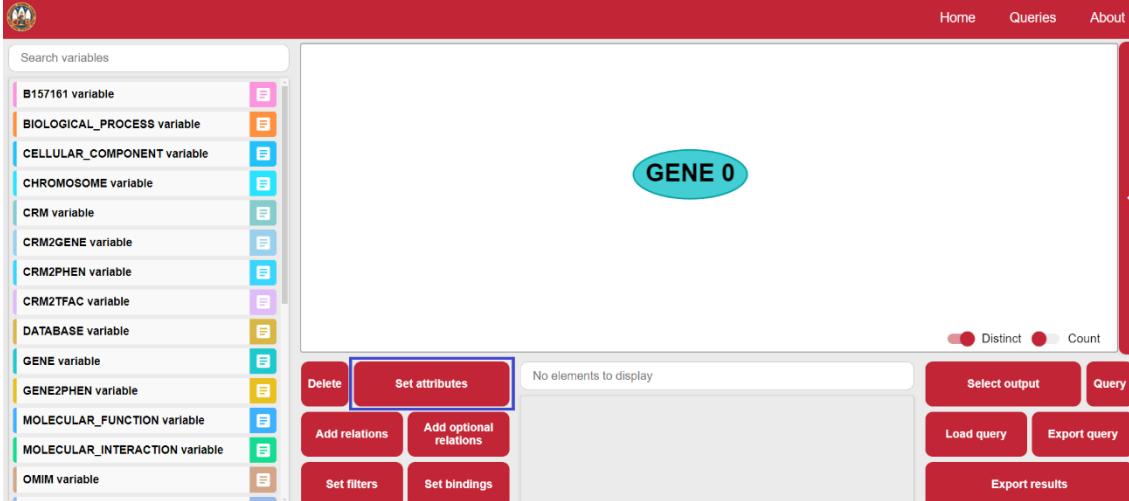
Some additional examples are given below:

- **Example 1:** Filtering by taxon.

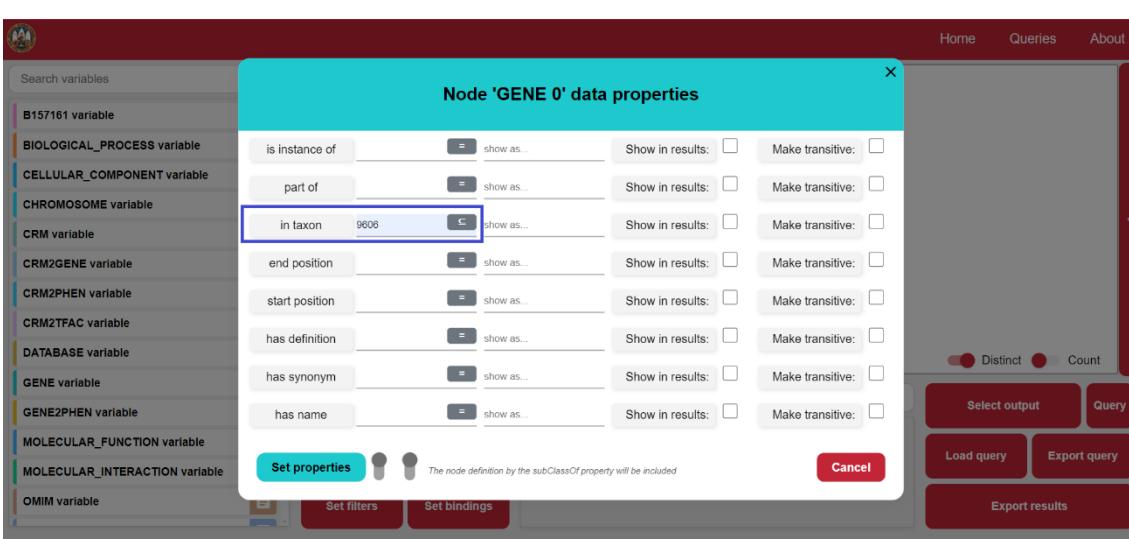
The resources in RDF are represented by Uniform Resource Identifiers (URIs), so these must be used when filtering a resource. This is the case for taxon (*in taxon* property, in "Set attributes"). Because URIs can be tedious to work with, e.g. "http://purl.obolibrary.org/obo/NCBITaxon_9606", the "content in" or " \subseteq " operator makes it easier to work with identifiers only. Below we include a table with the taxonomic IDs of the most relevant species included in BioGateway:

label	TAXON ID	URI_taxon
<i>Mus musculus</i>	10090	http://purl.obolibrary.org/obo/NCBITaxon_10090
<i>Arabidopsis thaliana</i>	3702	http://purl.obolibrary.org/obo/NCBITaxon_3702
<i>Oryza sativa Japonica Group</i>	39947	http://purl.obolibrary.org/obo/NCBITaxon_39947
<i>Dictyostelium discoideum</i>	44689	http://purl.obolibrary.org/obo/NCBITaxon_44689
<i>Zea mays</i>	4577	http://purl.obolibrary.org/obo/NCBITaxon_4577
<i>Caenorhabditis elegans</i>	6239	http://purl.obolibrary.org/obo/NCBITaxon_6239
<i>Danio rerio</i>	7955	http://purl.obolibrary.org/obo/NCBITaxon_7955
<i>Gallus gallus</i>	9031	http://purl.obolibrary.org/obo/NCBITaxon_9031
<i>Sus scrofa</i>	9823	http://purl.obolibrary.org/obo/NCBITaxon_9823
<i>Bos taurus</i>	9913	http://purl.obolibrary.org/obo/NCBITaxon_9913
<i>Homo sapiens</i>	9606	http://purl.obolibrary.org/obo/NCBITaxon_9606
<i>Drosophila melanogaster</i>	7227	http://purl.obolibrary.org/obo/NCBITaxon_7227
<i>Oryctolagus cuniculus</i>	9986	http://purl.obolibrary.org/obo/NCBITaxon_9986
<i>Rattus norvegicus</i>	10116	http://purl.obolibrary.org/obo/NCBITaxon_10116
<i>Saccharomyces cerevisiae</i> S288C	559292	http://purl.obolibrary.org/obo/NCBITaxon_559292
<i>Schizosaccharomyces pombe</i> 972h-	284812	http://purl.obolibrary.org/obo/NCBITaxon_284812
<i>Chlamydomonas reinhardtii</i>	3055	http://purl.obolibrary.org/obo/NCBITaxon_3055
<i>Plasmodium falciparum</i> 3D7	36329	http://purl.obolibrary.org/obo/NCBITaxon_36329
<i>Neurospora crassa</i> OR74A	367110	http://purl.obolibrary.org/obo/NCBITaxon_367110
<i>Canis lupus familiaris</i>	9615	http://purl.obolibrary.org/obo/NCBITaxon_9615

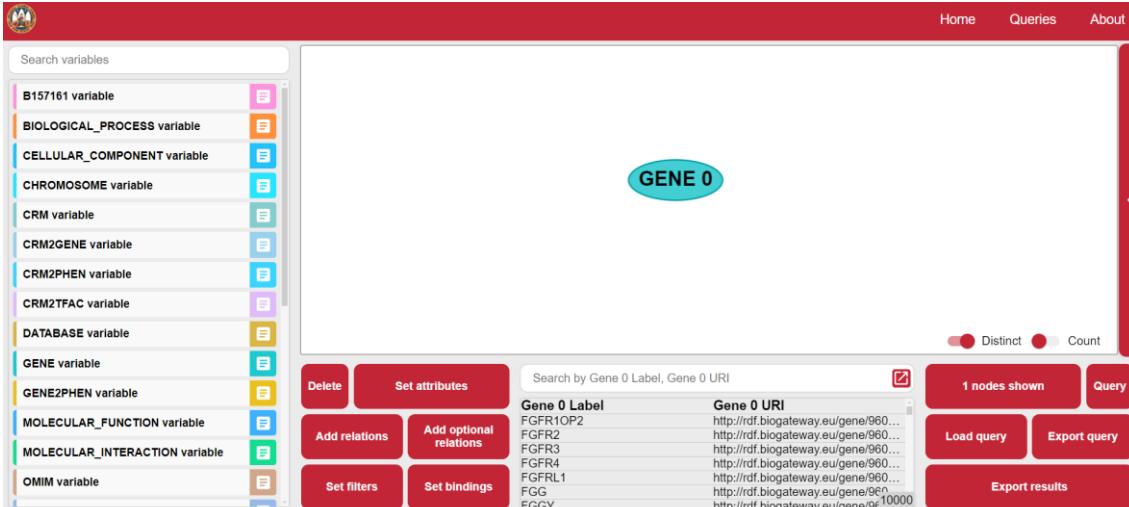
The following example illustrates the filtering of human genes using the taxon ID (9606):
What human genes does the network contain?

1. 

The interface shows a sidebar with a search bar and a list of variables. The variable 'GENE' is selected. A central panel displays a node labeled 'GENE 0' with several action buttons: Delete, Set attributes (which is highlighted), Add relations, Add optional relations, Set filters, and Set bindings.

2. 

A modal dialog titled 'Node 'GENE 0' data properties' is open. It lists various properties for the node: 'is instance of', 'part of', 'in taxon 9606', 'end position', 'start position', 'has definition', 'has synonym', and 'has name'. The 'in taxon' field has a value of '9606' and a 'show as...' button. Below the fields is a note: 'The node definition by the subClassOf property will be included'. At the bottom are 'Set properties' and 'Cancel' buttons.

3. 

The interface shows the results of the query. A search bar at the top right contains the text 'Search by Gene 0 Label, Gene 0 URI'. Below it, a table lists 'Gene 0 Label' and 'Gene 0 URI' for several entries. The table includes columns for 'Gene 0 Label' (e.g., FGFR1OP2, FGFR2, FGFR3, FGFR4, FGFRL1, FGG, FGCV) and 'Gene 0 URI' (e.g., http://rdf.biogateway.eu/gene/960...). A summary at the bottom indicates '1 nodes shown'.

- **Example 2:** Filtering by chromosome.

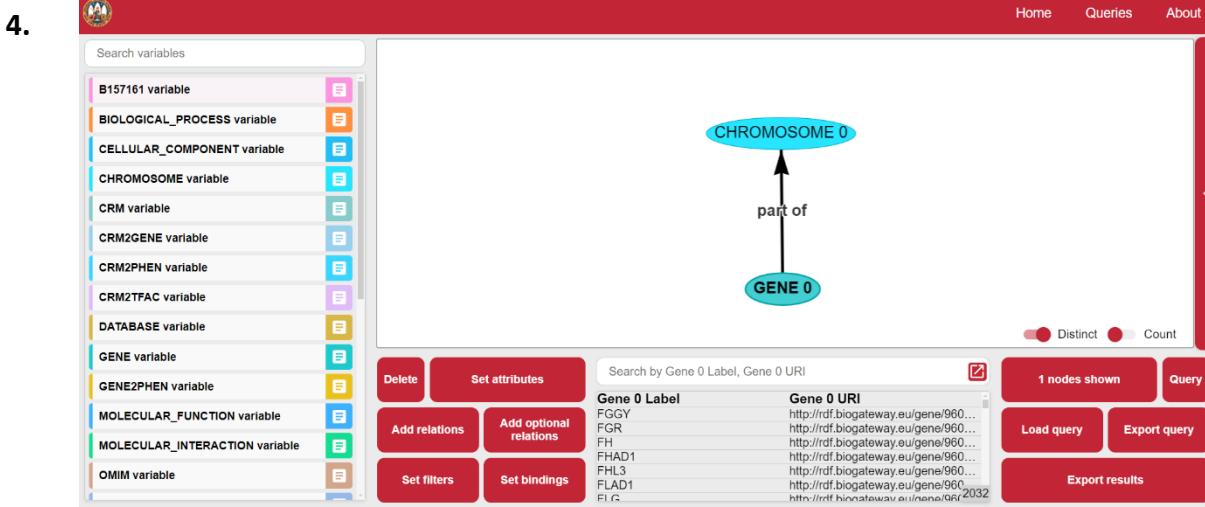
Chromosomes are entities available as variables, and are resources that have labels. Therefore, chromosomes can be filtered through their labels. Strings can be filtered in INTUITION using the " $=$ " (exact value) or " \subseteq " (contained in) operators. The default configuration of string filtering is not case-sensitive.

The following example filters human genes on chromosome 1 (*What human genes are located on chr-1?*).

1.

2.

3.

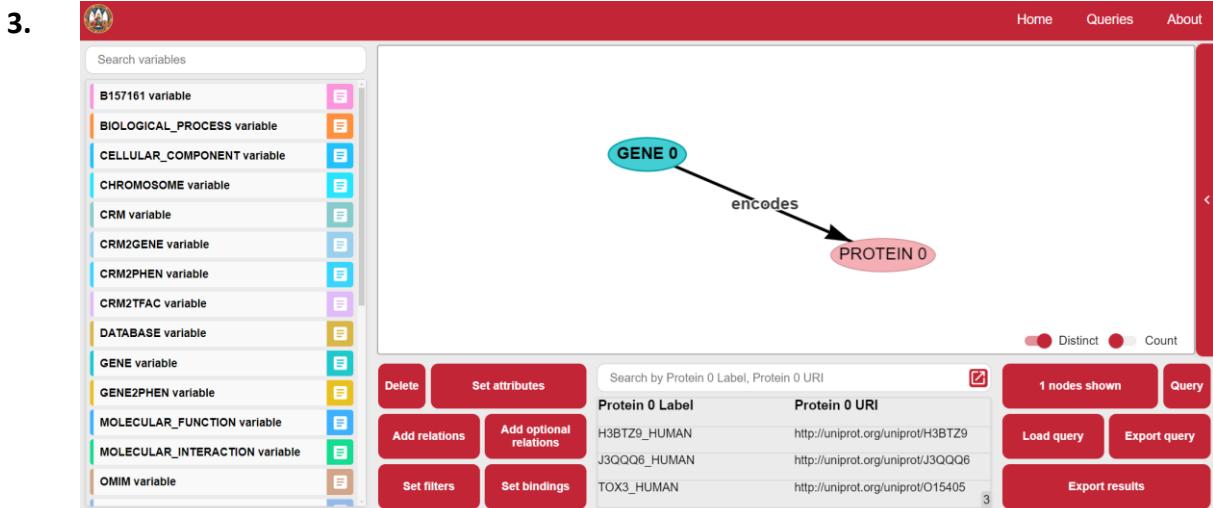


- Example 3: Filtering by name.

For this example we illustrate the query building to obtain the proteins encoded by the human TOX3 gene: *What proteins are encoded by the human TOX3 gene?* To do this, after including the link <Gene> <encodes> <Protein>, we modify the attributes of Gene node to indicate the name (TOX3) and the human taxon (9606).

1.

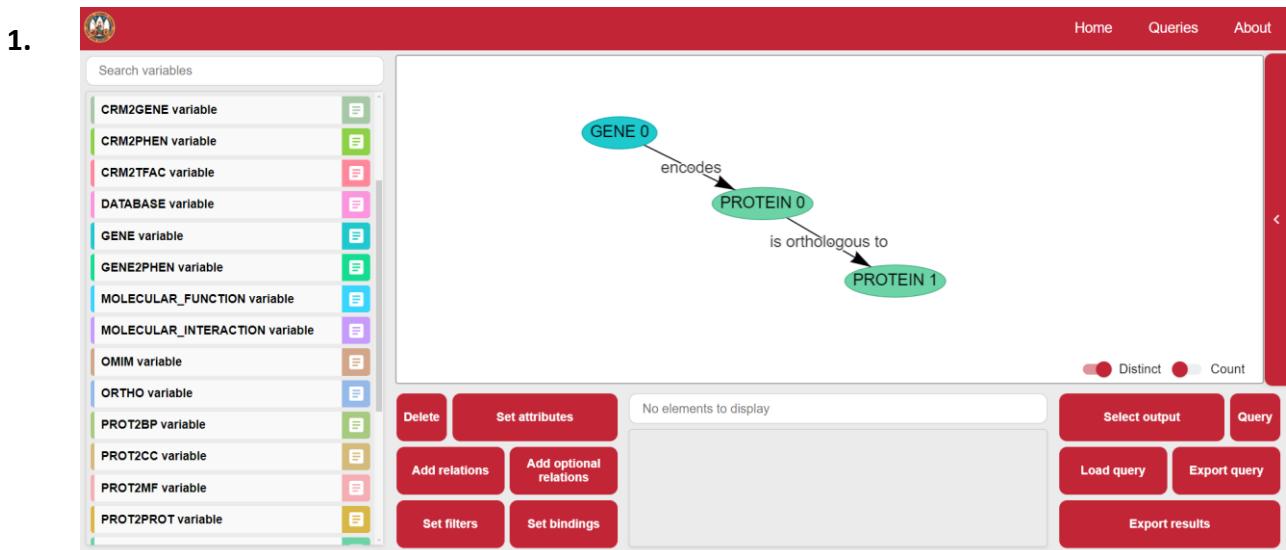
2.



5.2. Count and display unique results

The output table shows the biological entities that meet the biological selection criteria. Since a user can design complex query patterns and has the freedom to choose which entities they want to include in the output ("Select output" button), duplicate entities might appear in the result. For this reason, the "Distinct" button is activated for automatic filtering.

For example, we can query: *What are the orthologous proteins of the human TP53 gene?* To do this, we generate the relations <Gene> <encodes> <Protein>, and <Protein> <is orthologous to> <Protein>. Then we modify Gene's attributes to indicate the name and taxon.



2.

3.

If we include all the entities in the output, and examine the extended table of results, we can see the relation between the human TP53 gene, its protein products and orthologous proteins in other organisms.

4.

Gene 0 Label	Gene 0 URI	Protein 0 Label	Protein 0 URI	Protein 1 Label	Protein 1 URI
TP53	http://rdf.biogateway.eu/gene/9606/TP53	P53_HUMAN	http://uniprot.org/uniprot/P04637	A0A0B4VFS7_DANRE	http://uniprot.org/uniprot/A0A0B4VFS7
TP53	http://rdf.biogateway.eu/gene/9606/TP53	A0A087WT22_HUMAN	http://uniprot.org/uniprot/A0A087WT22	A0A4X1UD21_PIG	http://uniprot.org/uniprot/A0A4X1UD21
TP53	http://rdf.biogateway.eu/gene/9606/TP53	A0A087WXZ1_HUMAN	http://uniprot.org/uniprot/A0A087WXZ1	A0A4X1UD21_PIG	http://uniprot.org/uniprot/A0A4X1UD21
TP53	http://rdf.biogateway.eu/gene/9606/TP53	A0A087X1Q1_HUMAN	http://uniprot.org/uniprot/A0A087X1Q1	A0A4X1UD21_PIG	http://uniprot.org/uniprot/A0A4X1UD21
TP53	http://rdf.biogateway.eu/gene/9606/TP53	P53_HUMAN	http://uniprot.org/uniprot/P04637	P53_PIG	http://uniprot.org/uniprot/Q9TUB2
TP53	http://rdf.biogateway.eu/gene/9606/TP53	A0A087WT22_HUMAN	http://uniprot.org/uniprot/A0A087WT22	P53_PIG	http://uniprot.org/uniprot/Q9TUB2
TP53	http://rdf.biogateway.eu/gene/9606/TP53	A0A087WXZ1_HUMAN	http://uniprot.org/uniprot/A0A087WXZ1	P53_PIG	http://uniprot.org/uniprot/Q9TUB2
TP53	http://rdf.biogateway.eu/gene/9606/TP53	A0A087X1Q1_HUMAN	http://uniprot.org/uniprot/A0A087X1Q1	P53_PIG	http://uniprot.org/uniprot/Q9TUB2
TP53	http://rdf.biogateway.eu/gene/9606/TP53	P53_HUMAN	http://uniprot.org/uniprot/P04637	A0A0B4K7P1_DROME	http://uniprot.org/uniprot/A0A0B4K7P1
TP53	http://rdf.biogateway.eu/gene/9606/TP53	P53_HUMAN	http://uniprot.org/uniprot/P04637	B0R0M3_DANRE	http://uniprot.org/uniprot/B0R0M3
TP53	http://rdf.biogateway.eu/gene/9606/TP53	P53_HUMAN	http://uniprot.org/uniprot/P04637	B0S576_DANRE	http://uniprot.org/uniprot/B0S576
TP53	http://rdf.biogateway.eu/gene/9606/TP53	P53_HUMAN	http://uniprot.org/uniprot/P04637	B0S577_DANRE	http://uniprot.org/uniprot/B0S577
TP53	http://rdf.biogateway.eu/gene/9606/TP53	P53_HUMAN	http://uniprot.org/uniprot/P04637	G1K2L5_DANRE	http://uniprot.org/uniprot/G1K2L5
TP53	http://rdf.biogateway.eu/gene/9606/TP53	P53_HUMAN	http://uniprot.org/uniprot/P04637	A0A167VDT2_CHICK	http://uniprot.org/uniprot/A0A167VDT2
TP53	http://rdf.biogateway.eu/gene/9606/TP53	P53_HUMAN	http://uniprot.org/uniprot/P04637	F1P1U2_CHICK	http://uniprot.org/uniprot/F1P1U2
TP53	http://rdf.biogateway.eu/gene/9606/TP53	P53_HUMAN	http://uniprot.org/uniprot/P04637	D4AA88_RAT	http://uniprot.org/uniprot/D4AA88

The table contains a total of 51 entries/rows, corresponding to the results that satisfy the search pattern. However, we can see that several proteins encoded by the human TP53 gene are related to the same orthologous protein. Therefore, if we now only select as output the orthologous proteins, and we deactivate the "Distinct" button, we obtain the same 51 results that satisfy the search pattern, but with repeated values, because we are only selecting the orthologous proteins.

5.

Search variables

- CRM2GENE variable
- CRM2PHEN variable
- CRM2TFAC variable
- DATABASE variable
- GENE variable
- GENE2PHEN variable
- MOLECULAR_FUNCTION variable
- MOLECULAR_INTERACTION variable
- OMIM variable
- ORTHO variable
- PROT2BP variable
- PROT2CC variable
- PROT2MF variable
- PROT2PROT variable

Diagram: GENE 0 encodes PROTEIN 0, which is orthologous to PROTEIN 1.

Protein 1 Label	Protein 1 URI
A0A0B4VFS7_DANRE	http://uniprot.org/uniprot/A0A0B4VFS7
A0A4X1UD21_PIG	http://uniprot.org/uniprot/A0A4X1UD21
A0A4X1UD21_PIG	http://uniprot.org/uniprot/A0A4X1UD21
A0A4X1UD21_PIG	http://uniprot.org/uniprot/A0A4X1UD21
P53_PIG	http://uniprot.org/uniprot/Q9TUB2
P53_PIG	http://uniprot.org/uniprot/Q9TUB2
PRR_PIG	http://uniprot.org/uniprot/O9T1R2

Buttons: Delete, Set attributes, Add relations, Add optional relations, Set filters, Set bindings, Search by Protein 1 Label, Protein 1 URI, Distinct (selected), Count, 1 nodes shown, Query, Load query, Export query, Export results.

On the contrary, with the "Distinct" functionality activated (activated by default), we only obtain the unique results, which in this case are 23 (23 orthologous proteins).

6.

Search variables

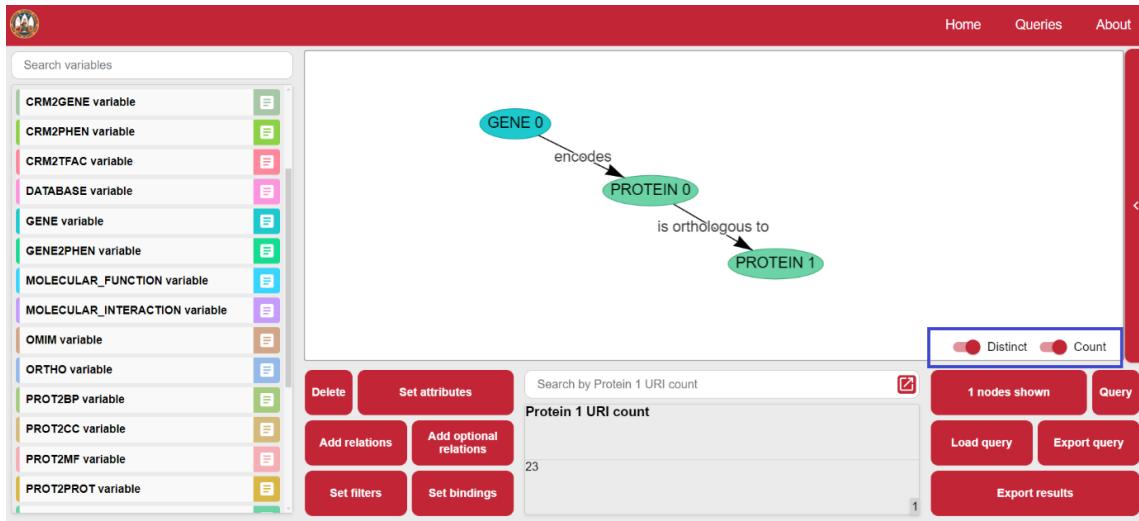
- CRM2GENE variable
- CRM2PHEN variable
- CRM2TFAC variable
- DATABASE variable
- GENE variable
- GENE2PHEN variable
- MOLECULAR_FUNCTION variable
- MOLECULAR_INTERACTION variable
- OMIM variable
- ORTHO variable
- PROT2BP variable
- PROT2CC variable
- PROT2MF variable
- PROT2PROT variable

Diagram: GENE 0 encodes PROTEIN 0, which is orthologous to PROTEIN 1.

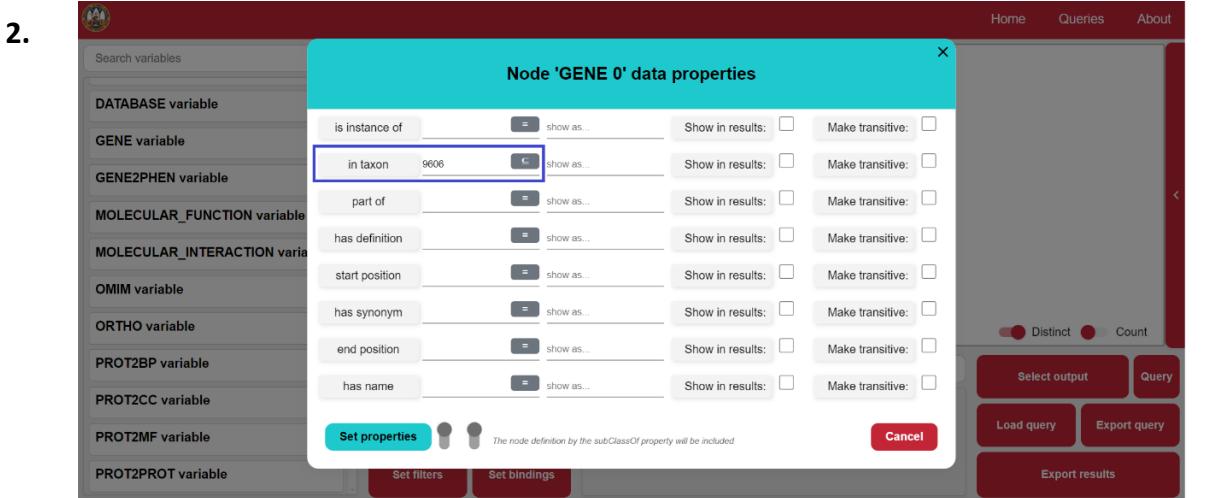
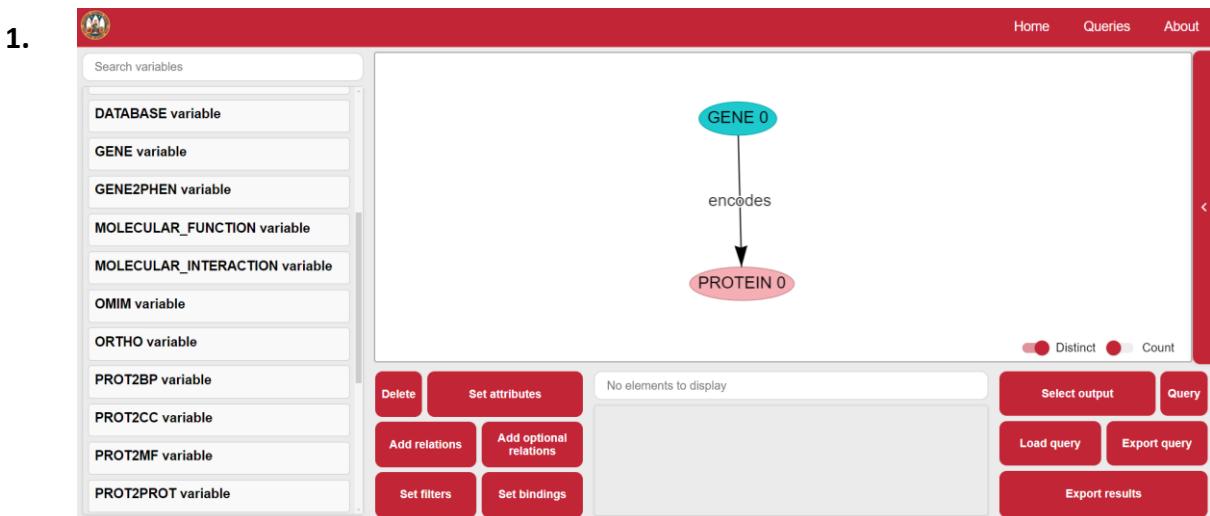
Protein 1 Label	Protein 1 URI
A0A0B4VFS7_DANRE	http://uniprot.org/uniprot/A0A0B4VFS7
A0A4X1UD21_PIG	http://uniprot.org/uniprot/A0A4X1UD21
P53_PIG	http://uniprot.org/uniprot/Q9TUB2
A0A0B4K7P1_DROME	http://uniprot.org/uniprot/A0A0B4K7P1
B0R0M3_DANRE	http://uniprot.org/uniprot/B0R0M3
B0S576_DANRE	http://uniprot.org/uniprot/B0S576
R0S577_DANRE	http://uniprot.org/uniprot/R0S577

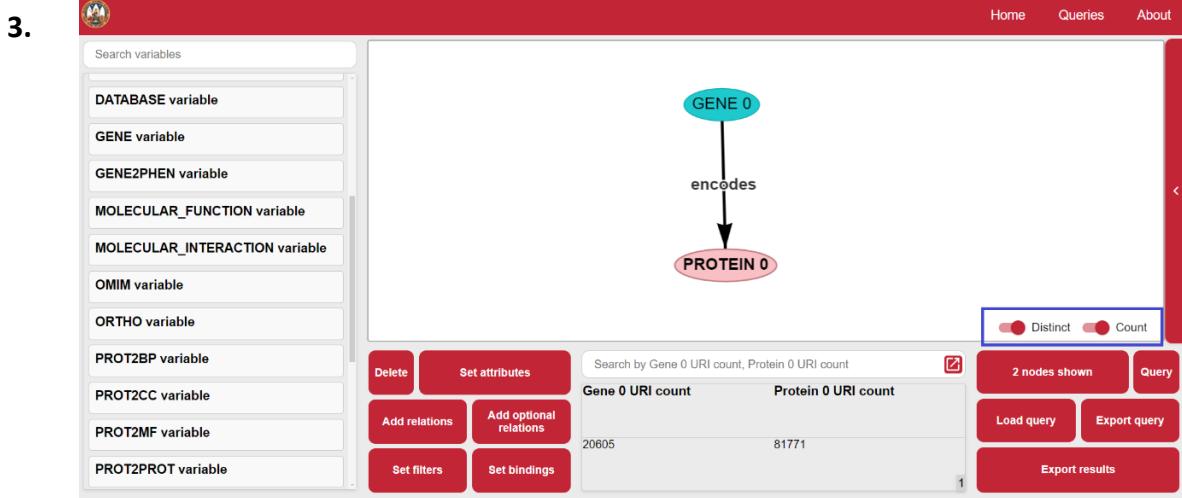
Buttons: Delete, Set attributes, Add relations, Add optional relations, Set filters, Set bindings, Search by Protein 1 Label, Protein 1 URI, Distinct (selected), Count, 1 nodes shown, Query, Load query, Export query, Export results.

On the other hand, activating the "Count" button displays the number of entities that fit the search pattern of the query.



Below we include another example. We can build the query: *How many human genes encode proteins, and how many proteins are there?*

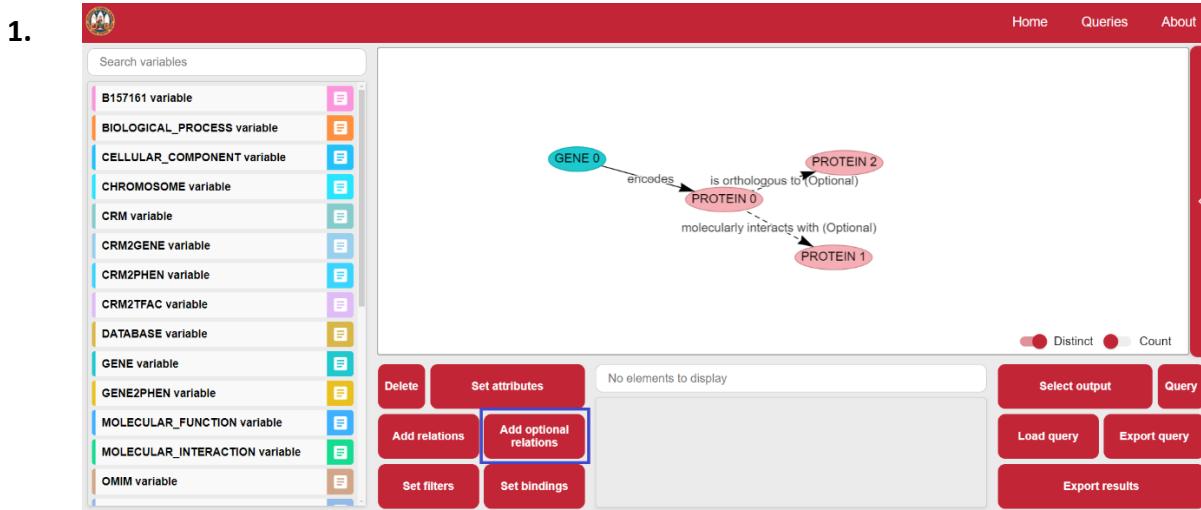




5.3. Optional relations

INTUITION also allows to include optional relations (“Add optional relations” button). As this is an optional pattern, the information is added if it exists, so it does not work as a filter.

In this way, INTUITION allows queries like: *What proteins are encoded by the human TOX3 gene? Do these protein products interact with any other proteins? Is there information about proteins orthologous to those encoded by the human TOX3 gene?*



2.

3.

Note: Queries can involve different variables of the same entity type. Queries may require handling the same entity as different variables, e.g. protein-protein interaction involves two different proteins, and therefore two different variables. INTUITION allows the inclusion of the same variable more than once. These nodes are numbered starting with 0. The counter is reset to zero when the application is updated, not when the node is deleted.

5.4. Multiple values

To avoid creating repetitive queries when the general structure of the query is the same, but the characteristics of the entities are different, INTUITION allows a user to assign different values to the variables. For example, if we are interested in searching for cis-regulatory modules (CRM) identified in two or more tissues of interest, we do not need to repeat the same query for each tissue.

When we want to add a relation between entities ("Add relations"), instead of selecting the general variable, we can use the "Enter URI values" box to specify several possible entities. First we insert an entity of interest, and then click on "+". Next, we can specify another entity of interest, and click on '+' again to include it. In this way we create a batch of possible values. This operation is repeated until the user has included all the desired

entities. When all the entities that the user wants to include have been added, we click "OK" to insert the entire stack of values as a single node.

As shown in the following example (*Which CRMs have been identified in heart and liver?*), we can specify different tissues in the "Enter URI values" box of "observed in" property. Click on "+" to include values and click on "OK" when all values are listed. As BioGateway uses semantic resources to identify entities, the values entered must be Uniform Resource Identifiers (URIs) corresponding to these resources. Below we provide a table with the main vocabularies used to facilitate the use of these URIs.

Biological entity	Vocabulary
Taxon	source/vocabulary: NCBI organismal classification prefix: http://purl.obolibrary.org/obo/NCBITaxon_ URI: prefix + taxon ID URI example: http://purl.obolibrary.org/obo/NCBTaxon_9606
CRM (cis-regulatory modules, currently only human enhancers)	source/vocabulary: BioGateway prefix: http://rdf.biogateway.eu/crm/ URI: prefix + taxon ID + crm ID URI example: http://rdf.biogateway.eu/crm/9606/CRMHS00000003515
Gene	source/vocabulary: BioGateway prefix: http://rdf.biogateway.eu/gene/ URI: prefix + taxon ID + gene symbol URI example: http://rdf.biogateway.eu/gene/9606/TOX3
Protein / Transcription factor	source/vocabulary: Uniprot prefix: http://uniprot.org/uniprot/ URI: prefix + uniprot ID URI example: http://uniprot.org/uniprot/H3BTZ9
TAD	source/vocabulary: BioGateway prefix: http://rdf.biogateway.eu/tad/ URI: prefix + taxon ID + tad ID URI example: http://rdf.biogateway.eu/tad/9606/TADHS00000020654
Chromosome	source/vocabulary: NCBI prefix: https://www.ncbi.nlm.nih.gov/nuccore/ URI: prefix + NCBI Reference Sequence URI example: https://www.ncbi.nlm.nih.gov/nuccore/NC_000002.12
Reference genome	source/vocabulary: NCBI prefix: https://www.ncbi.nlm.nih.gov/assembly/ URI: prefix + RefSeq assembly accession URI example: https://www.ncbi.nlm.nih.gov/assembly/GCF_000001405.26
Cellular component / Molecular function / Biological process	source/vocabulary: Gene Ontology (GO) prefix: http://purl.obolibrary.org/obo/ URI: prefix + GO ID URI example: http://purl.obolibrary.org/obo/GO_0005634
Cell line	source/vocabulary: Cell Line Ontology (CLO) prefix: http://purl.obolibrary.org/obo/ URI: prefix + CLO ID URI example: http://purl.obolibrary.org/obo/CLO_0003684
Cell type	source/vocabulary: Cell Ontology (CL) prefix: http://purl.obolibrary.org/obo/

	URI: prefix + CL ID URI example: http://purl.obolibrary.org/obo/CL_0000066
Anatomical structure	source/vocabulary: Uber-anatomy ontology (UBERON) prefix: http://purl.obolibrary.org/obo/ URI: prefix + UBERON ID URI example: http://purl.obolibrary.org/obo/UBERON_0000948
Strand of a genomic sequence	source/vocabulary: Feature Annotation Location Description Ontology (FALDO) prefix: http://biohackathon.org/resource/faldo# URI: prefix + ForwardStrandPosition/ReverseStrandPosition URI example: http://biohackathon.org/resource/faldo#ReverseStrandPosition
crm2gene (relations between CRMs and their target genes)	source/vocabulary: BioGateway prefix: http://rdf.biogateway.eu/crm2pgene/ URI: prefix + crm2gene ID (<i>entity_vocab!entityID--entity_vocab!entityID</i>) URI example: http://rdf.biogateway.eu/crm2pgene/bgw!CRMHS00000003517--hgncsymbol!9606/TBX5
crm2phen (relations between CRMs and phenotypes, currently only diseases)	source/vocabulary: BioGateway prefix: http://rdf.biogateway.eu/crm2phen/ URI: prefix + crm2phen ID (<i>entity_vocab!entityID--entity_vocab!entityID</i>) URI example: http://rdf.biogateway.eu/crm2phen/bgw!CRMHS00000003515--doid!1682
crm2tfac (relations between CRMs and transcription factors)	source/vocabulary: BioGateway prefix: http://rdf.biogateway.eu/crm2tfac/ URI: prefix + crm2tfac ID (<i>entity_vocab!entityID--entity_vocab!entityID</i>) URI example: http://rdf.biogateway.eu/crm2tfac/bgw!CRMHS00000003515--uniprot!Q99593
gene2phen (relations between genes and phenotypes)	source/vocabulary: BioGateway prefix: http://rdf.biogateway.eu/gene-phen/ URI: prefix + gene2phen ID (<i>entity_vocab!entityID--entity_vocab!entityID</i>) URI example: http://rdf.biogateway.eu/gene-phen/hgncsymb!AAAS--omim!231550
tfac2gene (relations between transcription factors and their target genes)	source/vocabulary: BioGateway prefix: http://rdf.biogateway.eu/reg2utrg/ URI: prefix + tfac2gene ID (<i>entity_vocab!entityID--entity_vocab!entityID</i>) URI example: http://rdf.biogateway.eu/reg2utrg/uniprot!Q99801--gene!9606/WIF1
prot2prot (molecular interactions between proteins)	source/vocabulary: BioGateway prefix: http://rdf.biogateway.eu/prot-prot/ URI: prefix + prot2prot ID (<i>entity_vocab!entityID--entity_vocab!entityID</i>) URI example: http://rdf.biogateway.eu/prot-prot/uniprot!B4FE73--uniprot!Q5GAN9
reg2targ (regulatory relations between proteins)	source/vocabulary: BioGateway prefix: http://rdf.biogateway.eu/reg2utrg/ URI: prefix + reg2targ ID (<i>entity_vocab!entityID--entity_vocab!entityID</i>) URI example: http://rdf.biogateway.eu/reg2utrg/uniprot!P15976--uniprot!P02549
ortho relations between proteins)	source/vocabulary: BioGateway prefix: http://rdf.biogateway.eu/ortho/ URI: prefix + ortho ID (<i>entity_vocab!entityID--entity_vocab!entityID</i>) URI example: http://rdf.biogateway.eu/ortho/uniprot!B1AQN2--uniprot!Q9VJ95
prot2cc (relations between proteins and their cellular components)	source/vocabulary: BioGateway prefix: http://rdf.biogateway.eu/prot-onto/ URI: prefix + prot2cc ID (<i>entity_vocab!entityID--entity_vocab!entityID</i>) URI example: http://rdf.biogateway.eu/prot-onto/uniprot!A0A023T778--obo!GO_0005634

prot2bp (relations between proteins and their molecular functions)	source/vocabulary: BioGateway prefix: http://rdf.biogateway.eu/prot-onto/ URI: prefix + prot2bp ID (<i>entity_vocab!entityID --entity_vocab!entityID</i>) URI example: http://rdf.biogateway.eu/prot-onto/uniprot!O70579--obo!GO_0035349
prot2mf (relations between proteins and their biological processes)	source/vocabulary: BioGateway prefix: http://rdf.biogateway.eu/prot-onto/ URI: prefix + prot2mf ID (<i>entity_vocab!entityID --entity_vocab!entityID</i>) URI example: http://rdf.biogateway.eu/prot-onto/uniprot!Q9ASK4--obo!GO_0004672

Example: Which CRMs have been identified in heart (UBERON_0000948) and liver (UBERON_0002107)?

1. Include the entity "CRM" and click on "Add relations".

The screenshot shows the BioGateway interface with the 'CRM' entity selected. The left sidebar lists various variable types, and the main area displays the CRM entity. A red box highlights the 'Add relations' button in the bottom right corner of the main panel.

2. Select the "observed in" property and use the "Enter URI values" box.

The screenshot shows the BioGateway interface with the 'observed in' property selected. A red box highlights the 'Enter URI values' input box in the dropdown menu. The input box contains the placeholder text '+ Enter URI values'.

3. Enter the first URI (http://purl.obolibrary.org/obo/UBERON_0000948) and click "+".

The screenshot shows the CRM 0 interface. On the left is a sidebar with a search bar and a list of variable types: B157161 variable, BIOLOGICAL_PROCESS variable, CELLULAR_COMPONENT variable, CHROMOSOME variable, CRM variable, CRM2GENE variable, CRM2PHEN variable, CRM2TFAC variable, DATABASE variable, GENE variable, GENE2PHEN variable, MOLECULAR_FUNCTION variable, MOLECULAR_INTERACTION variable, and OMIM variable. The CRM variable is selected. A context menu is open over the CRM variable, listing various relationships like 'is instance of', 'has source', etc. A modal dialog box is centered, containing a text input field with the URI http://purl.obolibrary.org/obo/UBERON_0000948, an 'OK' button, and a note stating 'No target class defined. Add it manually.' Below the modal is a message 'No elements to display'. At the bottom right of the interface are buttons for 'Select output', 'Query', 'Load query', 'Export query', and 'Export results'.

4. Enter the second URI (http://purl.obolibrary.org/obo/UBERON_0002107) and click "+".

This screenshot is similar to the previous one, showing the CRM 0 interface. The sidebar and context menu are identical. The modal dialog box now contains two URIs: http://purl.obolibrary.org/obo/UBERON_0000948 and http://purl.obolibrary.org/obo/UBERON_0002107. The 'OK' button is highlighted with a blue border. The rest of the interface and message below the modal are the same as in the previous screenshot.

5. Click "OK" to enter the entity batch.

This screenshot shows the CRM 0 interface after clicking 'OK'. The modal dialog box is closed, and the two URIs are listed in a new input field at the bottom of the modal: '+ Enter URI values'. The 'OK' button is now greyed out. The rest of the interface, including the sidebar, context menu, and bottom buttons, remains the same as in the previous screenshots.

6. Select the data output in "Select output" and click on "Query" to run the query.

The screenshot shows the OBOLLIBRARY interface with a search bar for variables. A query has been run, resulting in two nodes: CRM 0 and CRM 0. CRM 0 is connected to two URIs: http://purl.obolibrary.org/obo/UBERON_0000948 and http://purl.obolibrary.org/obo/UBERON_0002107. Below the results are buttons for 'Delete', 'Set attributes', 'Add relations', 'Add optional relations', 'Set filters', and 'Set bindings'. On the right, there are buttons for 'Select output' (highlighted), 'Query', 'Load query', 'Export query', and 'Export results'.

7. The results can be downloaded with "Export results", as well as the "Export query".

The screenshot shows the OBOLLIBRARY interface with a search bar for variables. A query has been run, resulting in two nodes: CRM 0 and CRM 0. CRM 0 is connected to two URIs: http://purl.obolibrary.org/obo/UBERON_0000948 and http://purl.obolibrary.org/obo/UBERON_0002107. Below the results are buttons for 'Delete', 'Set attributes', 'Add relations', 'Add optional relations', 'Set filters', and 'Set bindings'. On the right, there are buttons for 'Select output' (highlighted), 'Query', 'Load query', 'Export query', and 'Export results'. A 'Count' button is selected, and the results table shows '1 nodes shown'.

If we want to count the number of CRMs, we click on the 'Count' button to activate this counting functionality: *How many CRMs have been identified in heart (UBERON_0000948) and liver (UBERON_0002107)?*

The screenshot shows the OBOLLIBRARY interface with a search bar for variables. A query has been run, resulting in two nodes: CRM 0 and CRM 0. CRM 0 is connected to two URIs: http://purl.obolibrary.org/obo/UBERON_0000948 and http://purl.obolibrary.org/obo/UBERON_0002107. Below the results are buttons for 'Delete', 'Set attributes', 'Add relations', 'Add optional relations', 'Set filters', and 'Set bindings'. On the right, there are buttons for 'Select output' (highlighted), 'Query', 'Load query', 'Export query', and 'Export results'. A 'Count' button is selected, and the results table shows '1 nodes shown'.

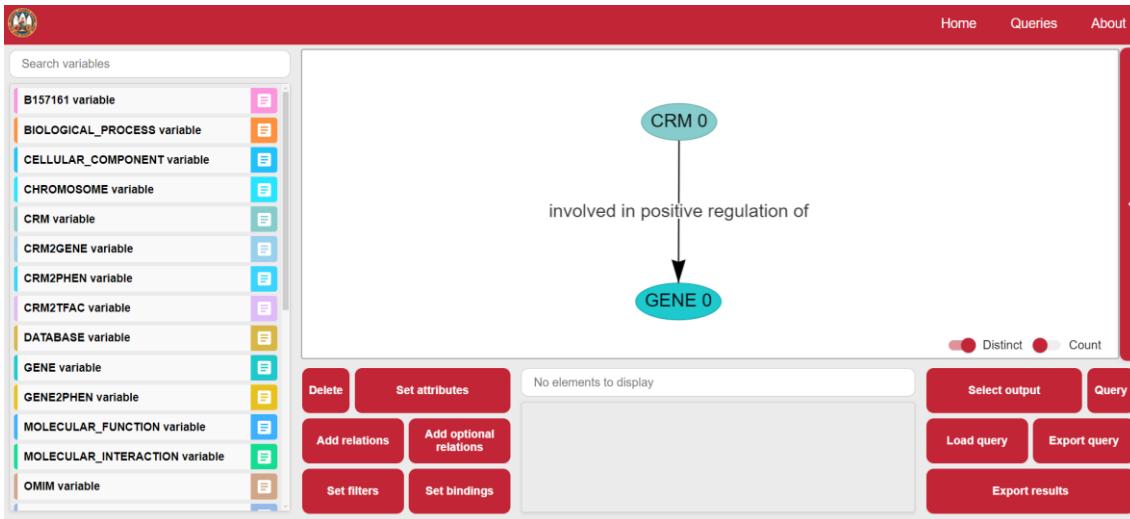
We can also add multiple values to the node that acts as the subject of the triplet:

5.5. Creating and filtering variables

INTUITION allow a user to create their own selection variables. This functionality is implemented in "Set bindings" button, in the "Pattern designer", and can be applied to attributes used in the query, renamed, or selected for output. To use an attribute in the search pattern, a value must be entered to act as a filter. To rename an attribute, simply change its name in "show as". To mark it for data output, check "Shown in results".

For example, by subtracting the end and start positions of the CRMs, and adding “1” to this number, we obtain the length of the sequences in a new variable. Then, we can filter this new variable in the “Set filters” button. Below we illustrate an example: *Which CRMs with a length less than or equal to 500 bp positively regulate the human TOX3 gene?* For this:

- First, we generate the relation <CRM> <involved in positive regulation of> <Gene>.



- Assign the attributes corresponding to the gene (name TOX3, and taxon).

The screenshot shows the 'Node 'GENE 0' data properties' dialog. It lists several attributes for 'GENE 0': 'is instance of', 'part of', 'in taxon' (with value '9606'), 'end position', 'start position', 'has definition', 'has synonym', and 'has name' (with value 'TOX3'). The 'has name' field is highlighted with a blue box. The dialog has a 'Set properties' button at the bottom.

- Select the CRM attributes that we are going to use to generate the new variables.

The screenshot shows the 'Node 'CRM 0' data properties' dialog. It lists several attributes for 'CRM 0': 'involved in pos...', 'in taxon', 'is instance of', 'is defined by', 'has definition', 'start position', 'end position', and 'has name'. The 'start position' and 'end position' fields are highlighted with blue boxes. The dialog has a 'Set properties' button at the bottom.

- Create the new variable in “Set bindings”.

CRM 0

Bindings and Variables

subtract End position CRM 0 - Start position CRM 0
Show in results Absolute

length subtract + Custom value (1)
Show in results Absolute

Variable length results from subtract + 1 Show in results Absolute Add binding

Set bindings Cancel Count

Delete Set attributes
Add relations Add optional relations
Set filters 2 bindings

Select output Query
Load query Export query
Export results

- We filter in ‘Set filters’ the new variable.

CRM 0

Filters

length <= 500
Filter length <= 500 Add

Set Filters Cancel Count

Delete Set attributes
Add relations Add optional relations
Set filters 2 bindings

Select output Query
Load query Export query
Export results

- Select the output and run the query:

CRM 0

involved in positive regulation of

GENE 0

Search by Crm 0 Label, Crm 0 URI, Start position CRM 0, End posit...
Crm 0 Label Crm 0 URI Start posit... End posit... Length
crm:CRMH... http://rdf.bio2rdf.org/resource/52609171 52609447 277
crm:CRMH... http://rdf.bio2rdf.org/resource/52455961 52456244 284
crm:CRMH... http://rdf.bio2rdf.org/resource/52492896 52493075 180
crm:CRMH... http://rdf.bio2rdf.org/resource/52524228 52524610 383
crm:CRMH... http://rdf.bio2rdf.org/resource/52530328 52530675 348
crm:CRMH... http://rdf.bio2rdf.org/resource/52545643 52545691 49
crm:CRMH... http://rdf.bio2rdf.org/resource/52751214 52751528 315
1 nodes shown Count
1 nodes shown Query
Load query Export query
Export results

5.6. Union of queries

INTUITION also allows the use of the UNION clause of SPARQL. UNION merges subqueries through common variables in both queries. We illustrate its use through a use case.

For example, we retrieve the OMIM entities that contain the string "breast cancer" as a name or synonym (*Which OMIM entities contain 'breast cancer' in their preferred label or alternative label?*), i.e. "name" and "synonym" are different attributes, but we can unite their values in a common variable using the UNION clause and a new unified rename for the attributes we want to unify ("label" in this example). To do that:

1. In the “Union builder” section, we create the graphs belonging to each of the subqueries, and we include an OMIM node in each of them. In the example, the graphs are "prefLabel" for the main label query and "altLabel" for the query of the synonym.
2. In each of the graphs we define the variable "label" according to the appropriate dataproperties ("has name" and "has synonym" properties, respectively). For this, we use the "show as" functionality, which enables to rename the variables, in this case under the common variable called "label".
3. We return to the main graph where we will join the two subqueries. For this, we include the subgraphs clicking on the green flap of each of the subgraphs.
4. Select one of the subgraphs represented as nodes and click on "Define union".
5. In "Node shown" we select the variables to be shown and in "Filters set" we filter the variable "label".
6. Run the query (Query).

1.

The screenshot shows the INTUITION interface in step 1. The left sidebar contains a list of variable types: B157161 variable, BIOLOGICAL_PROCESS variable, CELLULAR_COMPONENT variable, CHROMOSOME variable, CRM variable, CRM2GENE variable, CRM2PHEN variable, CRM2TFAc variable, DATABASE variable, GENE variable, GENE2PHEN variable, MOLECULAR_FUNCTION variable, MOLECULAR_INTERACTION variable, and OMIM variable. The 'OMIM 0' node is highlighted in the central workspace. On the right, a panel displays three subgraphs: 'Default', 'prefLabel', and 'altLabel'. The 'prefLabel' subgraph is currently selected. The bottom of the interface features a row of buttons: Delete, Set attributes, Add relations, Add optional relations, Set filters, Set bindings, Select output, Query, Load query, Export query, and Export results.

2.

Node 'OMIM 0' data properties

versionInfo show as... Show in results: Make transitive:
tui show as... Show in results: Make transitive:
rdf-schema#label show as... Show in results: Make transitive:
has synonym show as... Show in results: Make transitive:
Gene Symbol show as... Show in results: Make transitive:
MIMTYPEMEA... show as... Show in results: Make transitive:
has name **label** Show in results: Make transitive:
Moved from show as... Show in results: Make transitive:
core#notation show as... Show in results: Make transitive:

Set properties **Cancel**

Node 'OMIM 0' data properties

versionInfo show as... Show in results: Make transitive:
tui show as... Show in results: Make transitive:
rdf-schema#label show as... Show in results: Make transitive:
has synonym **label** Show in results: Make transitive:
Gene Symbol show as... Show in results: Make transitive:
MIMTYPEMEA... show as... Show in results: Make transitive:
has name show as... Show in results: Make transitive:
Moved from show as... Show in results: Make transitive:
core#notation show as... Show in results: Make transitive:

Set properties **Cancel**

3.

Home Queries About

Search variables

- B157161 variable
- BIOLOGICAL_PROCESS variable
- CELLULAR_COMPONENT variable
- CHROMOSOME variable
- CRM variable
- CRM2GENE variable
- CRM2PHEN variable
- CRM2TFAC variable
- DATABASE variable
- GENE variable
- GENE2PHEN variable
- MOLECULAR_FUNCTION variable
- MOLECULAR_INTERACTION variable
- OMIM variable

Define new graph +

- Default
- prefLabel**
- altLabel

prefLabel altLabel

Delete Set attributes Add relations Add optional relations Set filters Set bindings

No elements to display

Select output Query Load query Export query Export results

4.

Home Queries About

Search variables

- B157161 variable
- BIOLOGICAL_PROCESS variable
- CELLULAR_COMPONENT variable
- CHROMOSOME variable
- CRM variable
- CRM2GENE variable
- CRM2PHEN variable
- CRM2TFAC variable
- DATABASE variable
- GENE variable
- GENE2PHEN variable
- MOLECULAR_FUNCTION variable
- MOLECULAR_INTERACTION variable
- OMIM variable

Define new graph +

- Default
- prefLabel**
- altLabel

UNION

Delete Set attributes Add relations Add optional relations Union with graph 'altLabel' bindings

No elements to display

Select output Query Load query Export query Export results

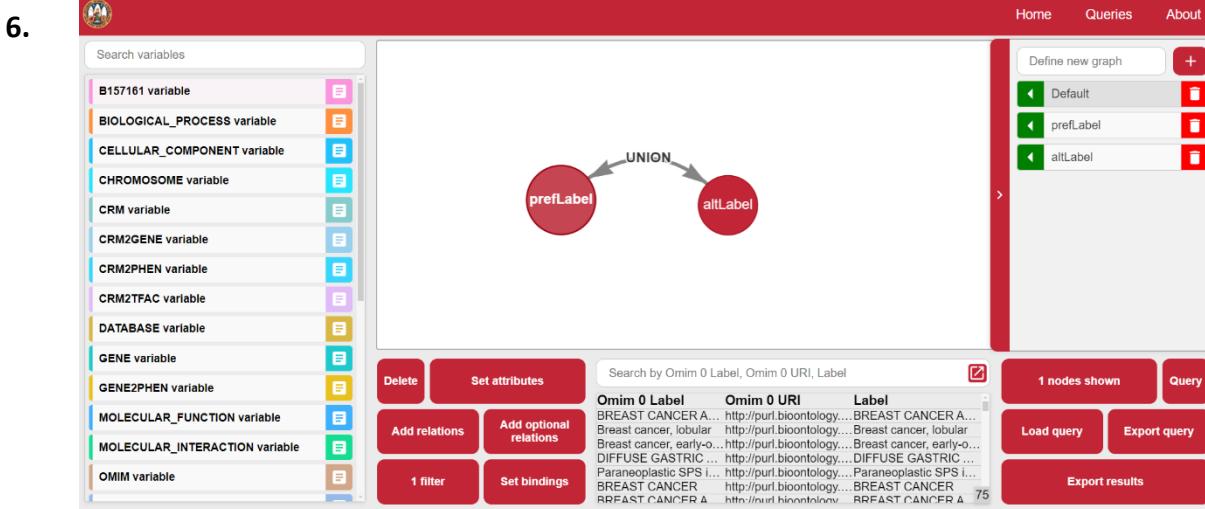
5.

Filters

label ⚡ breast cancer

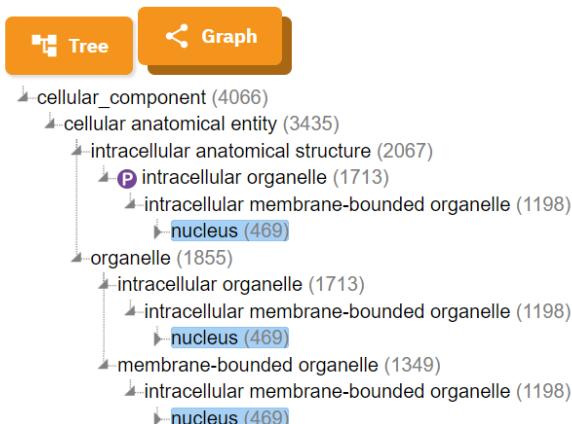
Filter label ⚡ breast cancer **Add**

Set Filters **Cancel**



5.7. Transitivity in INTUITION

Transitivity is a functionality that allows inferring relations between entities through existing relations between other entities, i.e. if an entity A is related to an entity B, and B is related to an entity C, it is possible to infer that A is related to C. For example, ontologies usually have a hierarchical structure. Gene Ontology (GO) is one of the ontologies imported into BioGateway and has a hierarchical structure of entities. GO has three hierarchically superior entities (biological process, cellular component and molecular function) which hold the other entities of the ontology. Thus, although the entity "nucleus" is not directly a subclass of the entity "cellular component", this relation can be inferred because "nucleus" is a subclass of an entity that inherits from "cellular component", with independence of the number of intermediate entities. Next, we illustrate this example with the hierarchical structure of this entity in GO, obtained by searching in the OLS Ontology portal:



INTUITION automatically identifies hierarchically superior entities existing in the knowledge network, to present them to the user as variables available for use. The entities modelled in BioGateway (Section 9.3) are subclasses of a main entity used as a variable. This design was chosen to ease the user's exploitation of the data. In contrast, imported ontologies have a complex hierarchy. Then, we recall the variables corresponding to imported ontologies:

- OMIM variable: entities from OMIM ontology (mainly phenotypes).

- Molecular_interaction: entities from Molecular Interactions ontology (MI).
- Cellular_component variable: cellular components from Gene Ontology (GO).
- Molecular_function variable: molecular functions from GO.
- Biological_process variable: biological processes from GO.
- Root variable: top hierarchically class of NCBI Taxon Ontology.
- Taxonomic_rank variable: top hierarchically class of NCBI Taxon Ontology.

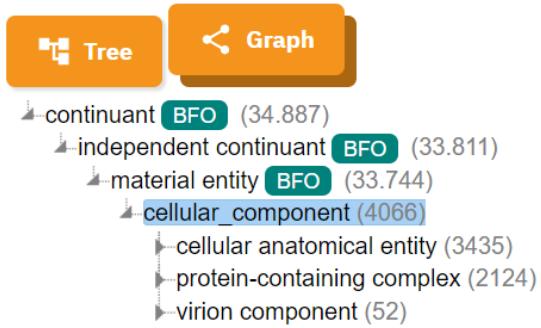
If we want to query *What cellular components does GO contain?* We can select the variable of interest (cellular component), include it for output ("Select output") and execute the query.

1.

2.

Cellular_component 0 Label	Cellular_component 0 URI
protein-containing complex	http://purl.obolibrary.org/obo/GO_0...
virion component	http://purl.obolibrary.org/obo/GO_0...
cellular anatomical entity	http://purl.obolibrary.org/obo/GO_0...

This query returns three entities (protein-containing complex, virion component, cellular anatomical entity) that correspond to the three entities that directly inherit from the GO cellular component entity:



On the other hand, if we want to query which cellular components GO contains, regardless of the hierarchy level, we must run a transitive query. For this purpose, after including the variable "cellular component", we go to its attributes and activate the button next to "Set properties" ("The node definition by the subClassOf property will be included and transitive"). This functionality makes the property "is subclass of" transitive.

1.

2.

The Node 'CELLULAR_COMPONENT 0' data properties dialog box contains the following properties:

- is instance of
- has_alternativ...
- database_cross_re...
- has_exact_syn...
- has_related_s...
- definition
- has_narrow_s...
- has_obo_nam...
- rdf-schema#label

For each property, there are fields for 'show as...' and checkboxes for 'Show in results:' and 'Make transitive:'.

3.

The screenshot shows the CellMiner interface with a search bar containing 'cellular' and a variable dropdown set to 'CELLULAR_COMPONENT variable'. The main area displays a single result node 'CELLULAR_COMPONENT 0' with a cyan oval highlight. Below the node, a table lists its properties and values. On the right side, there are buttons for 'Delete', 'Set attributes', 'Add relations', 'Add optional relations', 'Set filters', and 'Set bindings'. A search bar for 'Cellular_component 0 Label, Cellular_component 0 URI' is also present. The bottom right corner shows buttons for '1 nodes shown', 'Query', 'Load query', 'Export query', and 'Export results'. A legend indicates 'Distinct' (red dot) and 'Count' (grey dot).

This way, instead of three results we get the 4061 cellular components, regardless of the hierarchy level.

If we want to make transitive a property of the attributes, we just have to check the related button next to the attribute.

The screenshot shows a modal dialog titled 'Node 'CELLULAR_COMPONENT 0' data properties'. It lists various properties for the node, each with a 'Show in results:' checkbox and a 'Make transitive:' checkbox. The properties include 'is instance of', 'has_alternativ...', 'database_cross_reference', 'has_exact_syn...', 'has_related_s...', 'definition', 'has_narrow_s...', 'has_obo_nam...', and 'rdf-schema#label'. A note at the bottom states: 'The node definition by the subClassOf property will be included and transitive'. At the bottom left is a 'Set properties' button, and at the bottom right is a 'Cancel' button.

Here is another example involving transitivity: *In which cellular components is the human TP53 gene found?* To do this, we create the <Gene> <part of> <Cellular_component> relation. We then include the name and taxon of the gene in the Gene attributes. We select the data output and run the query.

1.

2.

3.

We return only one result (protein-containing complex), which is a direct subclass of "cellular component". To obtain all the results regardless of the hierarchy, we apply transitivity to the variable "cellular component":

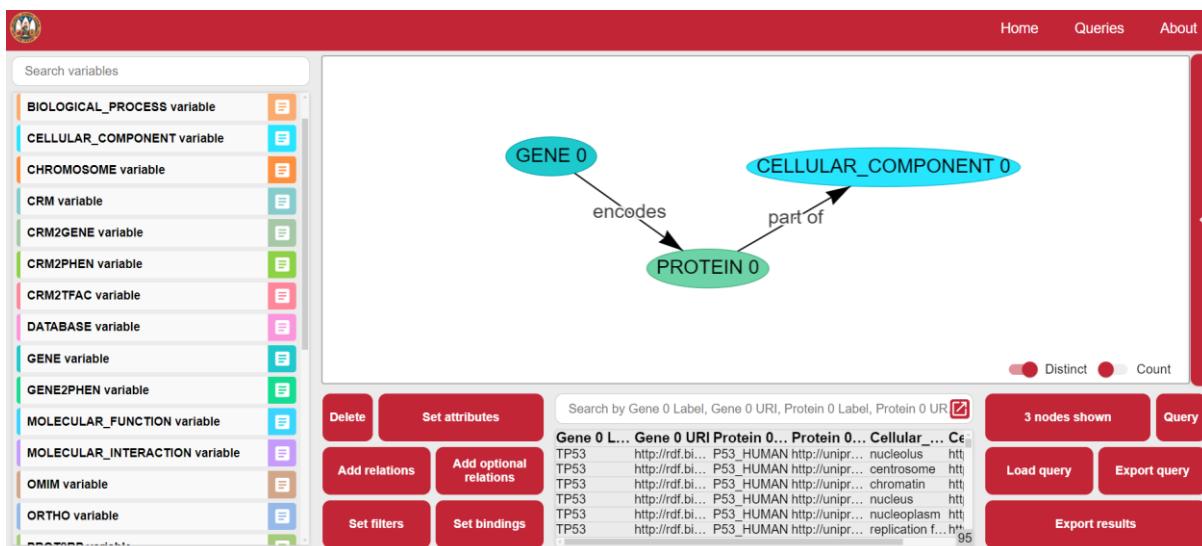
4.

5.

Complex queries which involve transitivity on variables that participate in relations can saturate the available memory. Therefore, the second button next to "Set properties" includes an optimised functionality for these cases (transitivity applied to variables taking part in relations).

6.

7.



6. Use Cases

The following Use Cases were developed in the paper "*Integration of chromosome locations and functional aspects of enhancers and topologically associating domains in knowledge graphs enables versatile queries about gene regulation*". The corresponding queries are attached for reproducibility and as examples of use. These use cases include complex queries that connect multiple nodes, use different filters, create variables, and join queries, so we recommend their consultation for a deeper understanding of the concepts introduced here for the graphical query building.

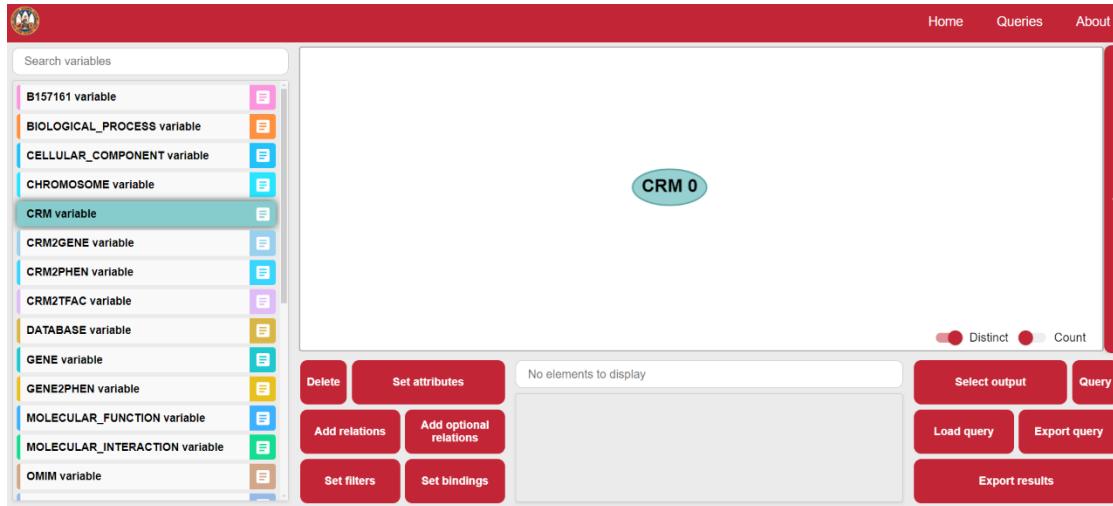
1. Use case 1: json files to load [here](#).
2. Use case 2: json files to load [here](#).
3. Use case 3: json files to load [here](#).

Query execution times differ between use cases. Next, we include a table with an approximate query time.

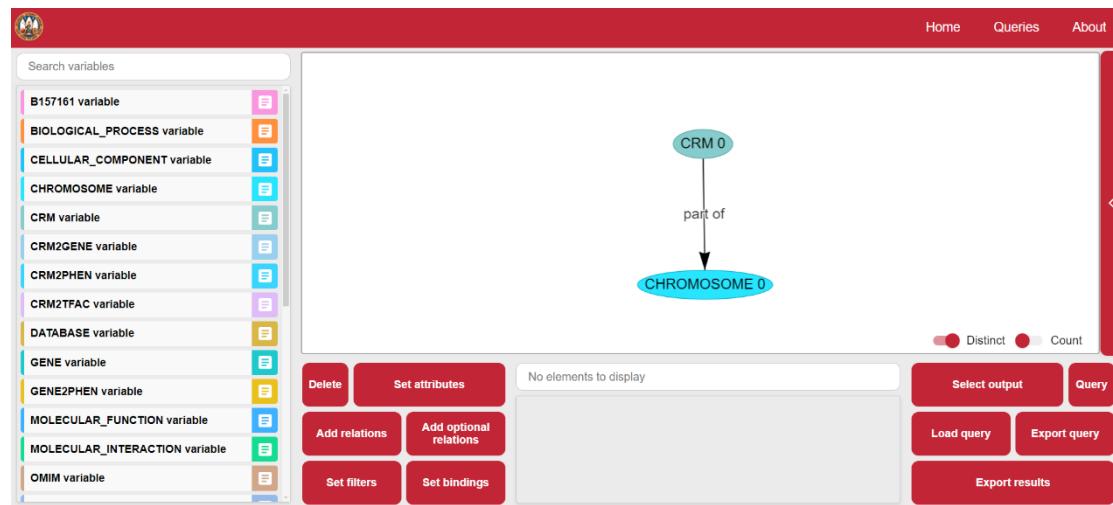
Query (Use Case – Query)	INTUITION query time (s)
UC1 - Q1	4
UC1 - Q2	26
UC1 - Q.3.1	2
UC1 - Q.3.2	3
UC1 - Q.3.3	1408
UC1 - Q.4.1	25
UC1 - Q.4.2	25
UC1 - Q.5.1	4
UC1 - Q.5.2	1
UC1 - Q.5.3	1602
UC2 - Q.1	10
UC2 - Q.2	3
UC2 - Q.3.1	8
UC2 - Q.3.2	728
UC2 - Q.4	2
UC2 - Q.5	2
UC3 - Q1	9

A guided step-by-step guide to building Use Case 1.1 is shown below: *Is the rs4784227 mutation (chr16:52565276) located in any enhancer sequence linked to target genes in the network? What databases support the sequence and what are their target genes? Is the enhancer related to any disease? Which proteins are encoded by the genes?*

- First, we insert the CRM node by clicking on the CRM variable (“Variable browser” section).



- We link the CRM to the chromosome variable (“Add relations” button).



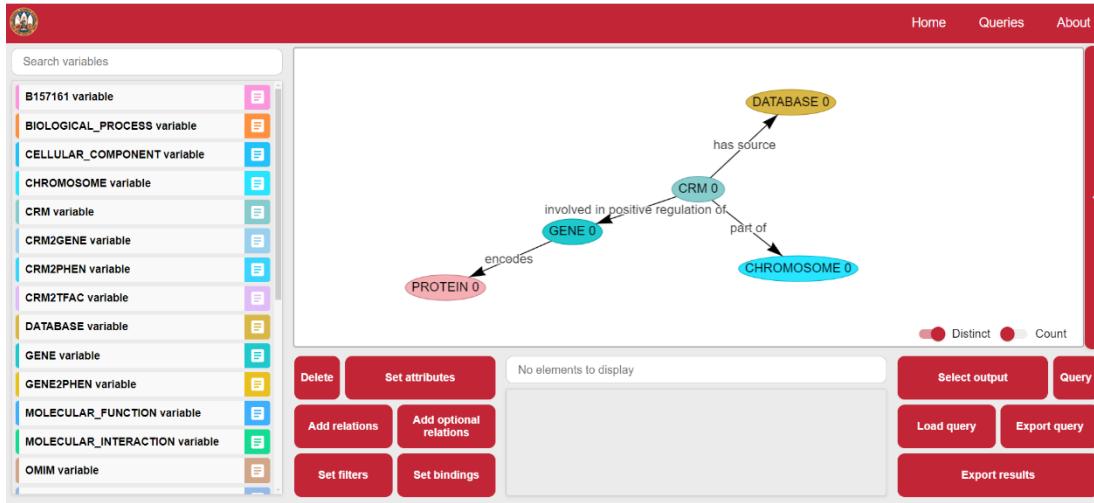
- And modify the attributes of both variables to select only those CRMs that overlap with the mutation (chr16:52565276) (“Set attributes” button).

The image displays two separate dialog boxes for setting properties of nodes "CRM 0" and "CHROMOSOME 0".

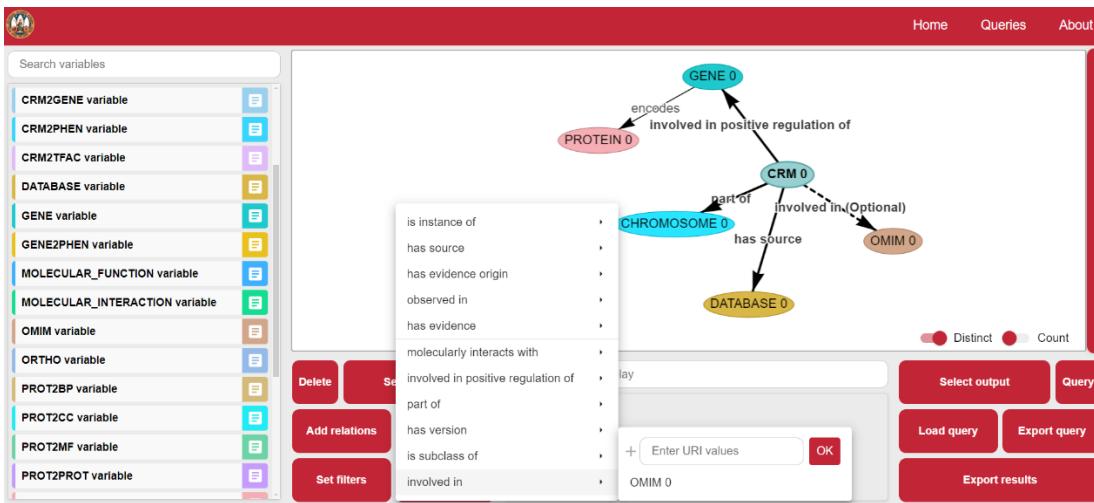
Node 'CRM 0' data properties: This dialog lists various properties for the CRM node. Several properties have their values set to "52565276": "start position" and "end position". The "has name" property is also present. Each property has checkboxes for "Show in results" and "Make transitive". A note at the bottom states: "The node definition by the subClassOf property will be included". Buttons at the bottom include "Set properties" (highlighted with a blue border) and "Cancel".

Node 'CHROMOSOME 0' data properties: This dialog lists properties for the chromosome node. It includes "is instance of", "has name" (set to "chr-16"), and "category". Similar to the CRM dialog, it has checkboxes for "Show in results" and "Make transitive". A note at the bottom states: "The node definition by the subClassOf property will be included". Buttons at the bottom include "Set properties" and "Cancel".

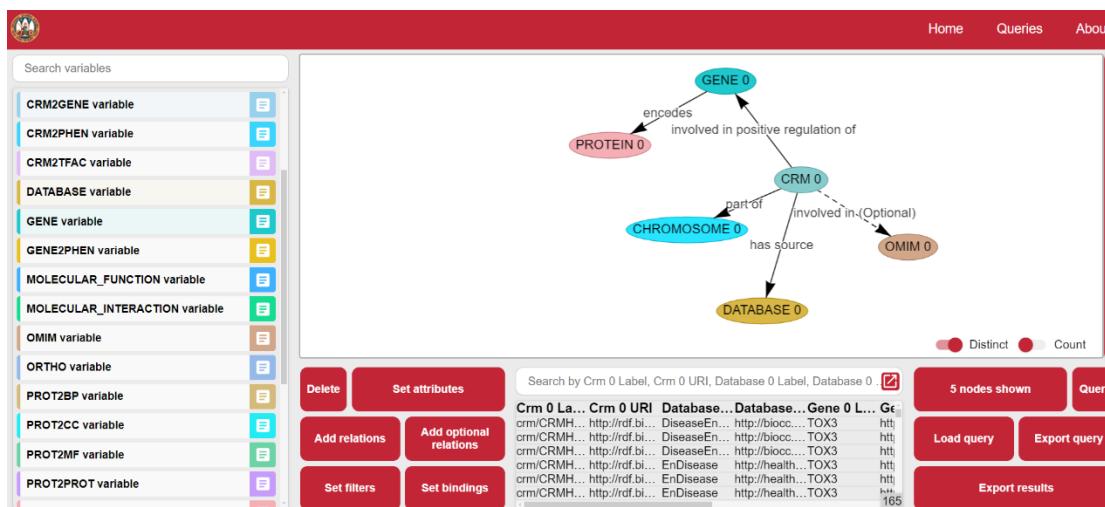
- We link the CRM entity with its database and target genes. We also link the genes to their encoded proteins (“Add relations” button).



- We include the relation between CRM and phenotype as an optional pattern (information that is included additionally and does not act as a filter) (“Add optional relations” button).



- Select the output data of interest (“Select output”) and run the query (“Query”).



- Finally, we can expand the results table, save the results table (“Export results”) and save the generated query (“Export query”).