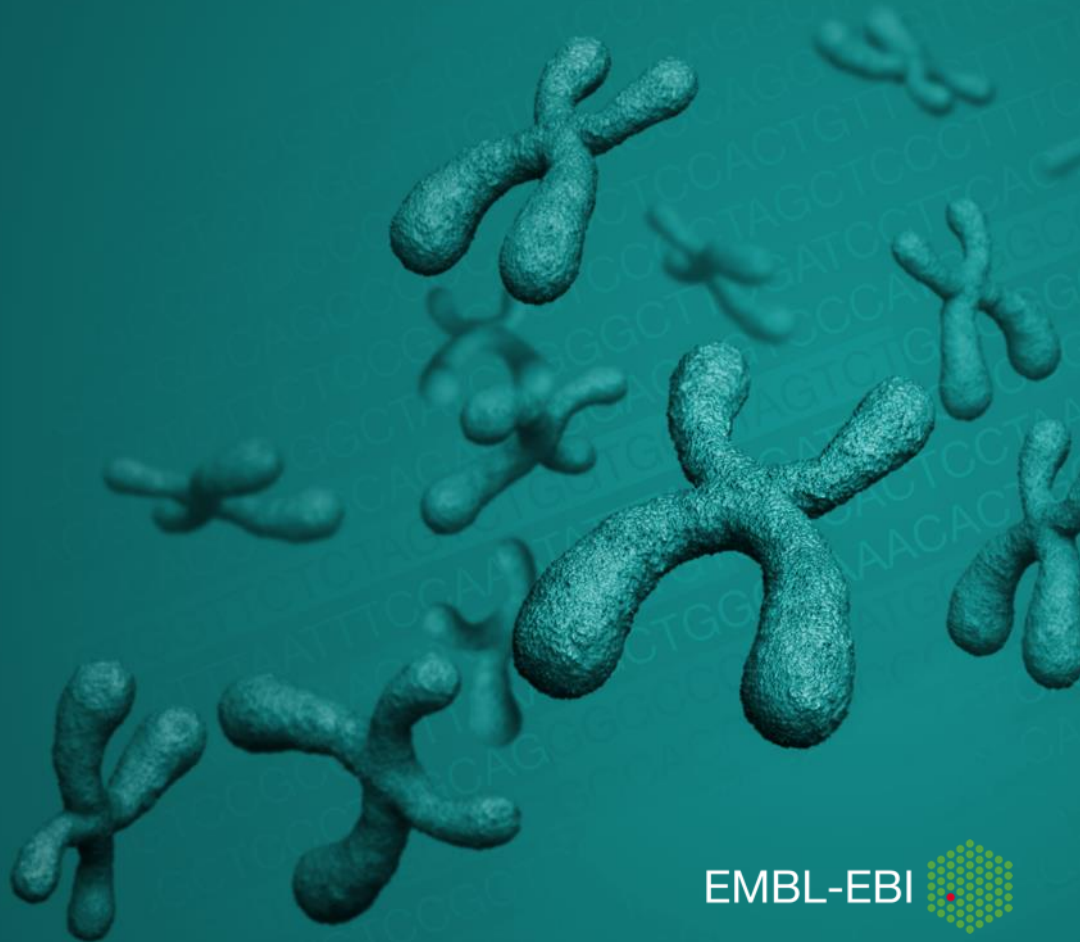


Gene Ontology Annotation Extensions

Increasing the expressivity of GO

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The Gene Ontology scope

- Molecular Function, e.g. *kinase activity, opsin binding*
- Biological Process, e.g. *cell cycle, limb development*
- Cellular Component, e.g. *nucleus, SMAD protein complex*

GO annotation practice

- Each GO annotation can pair only a single gene product with a single GO term
- Limits the complexity of information that can be captured
- Annotations cannot be linked

Cannot capture:

- Targets of a process/function,
e.g. hcn1 is phosphorylated by the serine/threonine kinase cdc2
- Localization dependency,
e.g. protein 'x' acts as a protein kinase in the nucleus but not the cytoplasm
- Enzyme substrates or products,
e.g. epsin-1 ubiquitination
- Processes involved in other processes,
e.g. localization of protein to nucleus in response to oxidative stress

GO annotation practice

- GO terms can be pre-composed for some of these, e.g. “protein localization to nucleus in response to oxidative stress”

But, we shouldn't attempt to make a term for *everything*

GO terms will always be a *subset* of total set of possible descriptions

New!

Annotation Extensions

Allows curators to combine GO terms with:

- other GO terms
- terms from external ontologies
- database identifiers representing genes or their products

That is, post-composition at the time of annotation

Semantics

Each annotation extension consists of a relationship-identifier pair, e.g.

occurs_in(CL:0000066)

Relationship Identifier



Each relationship has usage restrictions

- The primary GO terms (Col.5 of GAF) that can be used with the relationship
- The identifiers that may be used in the extension

Note: the extension provides the relationship of the GO term to other entities
NOT of the gene product to other entities

Semantics - example

e.g. *occurs_in*

- can only be used when annotating with GO:molecular function or GO:biological process
- is restricted to use with identifiers from cell type ontology (CL), anatomical ontology (UBERON), plant anatomical ontology (PO), C. elegans cell or anatomy ontology (WBbt) or GO:cellular component

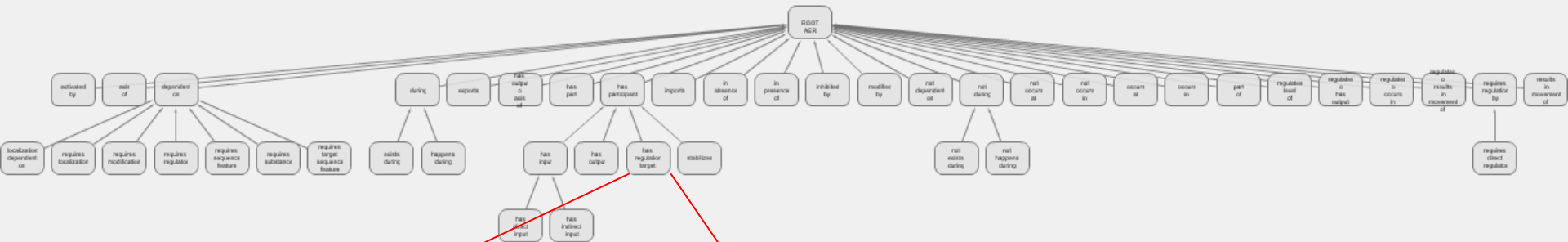
```
AMACR GO:0008111 IMP PMID:10655068 occurs_in(CL:0000057)
```

where GO:0008111 is alpha-methylacyl-CoA racemase activity (molecular function) and CL:0000057 is fibroblast (cell type ontology)

Semantics

- Over 40 **relationships** have been defined so far – more can be added
- Legal **identifiers** currently include:
 - ChEBI
 - Cell Type (CL)
 - Tissue Type (Uberon)
 - Sequence Ontology (SO)
 - Protein Ontology (PR)
 - Protein Complexes (MI)
 - Plant Ontology (PO)
 - Zebrafish development stages (ZFS)
 - *C. elegans* cell and anatomy ontology (WBbt)
 - Protein modifications (MOD)
 - Gene Ontology (GO)
 - Gene/protein identifiers (Ensembl, UniProt, PomBase etc.)
- more can be added

Graphical visualisation of relations



has_regulation_target

GOC wiki page: [has regulation target](#)

Domain: GO:0065007 (biological regulation)

Range: CHEBI:24431 (chemical entity) or GO:0032991 (macromolecular complex) or MI:0315 (protein complex) or PR:000000001 (protein) or SO:0000673 (transcript) or SO:0000704 (gene)

Definition: Identifies an entity (such as a gene, gene product, or complex) affected by a regulation Biological Process or regulator Molecular Function.

Independent and conjunctive extensions

Independent extensions (OR operator) are used to make separate statements about the same GO term, e.g. where a gene product can perform its activity in multiple places or under various conditions

“Pap1 is a transcription factor that regulates transcription of several oxidative stress response genes, including *trr1*, *pmd1*, *obr1*, *bfr1* and *ctt1*”

Pap1 GO:0045893 (positive regulation of transcription) IDA PMID:9585505

Annotation extensions are pipe separated:

```
has_regulation_target(PomBase:SPBC3F6.03)|has_regulation_target(PomBase:SPCC663.03)|  
has_regulation_target(PomBase:SPAC3C7.14c)|has_regulation_target(PomBase:SPCC18B5.01c)|  
has_regulation_target(PomBase:SPCC757.07c)
```

This is equivalent to making five separate annotations

Independent and conjunctive extensions

Conjunctive extensions (AND operator) are used to make linked statements about the same GO term where two or more extensions apply simultaneously, e.g. when a gene product acts upon a second gene product during the course of another process

Example 1:

“Upon oxidative stress, Sty1 regulates the nuclear localization of Pap1”

Sty1 GO:0034504 (protein localization to nucleus) IMP PMID:9585505

Annotation extensions are comma separated:

happens_during(GO:0034599),has_input(UniProtKB:Q01663)

Where GO:0034599 is ‘cellular response to oxidative stress’ and Q01663 is Pap1

Independent and conjunctive extensions

Conjunctive extensions

Example 2:

“TMEM115 is located in the nucleus that is part of an epithelial cell that is part of the cervix epithelium”

TMEM115 GO:0005634 (nucleus) IDA PMID:17973242

Annotation extensions are comma separated:

part_of(CL:0000066),part_of(UBERON:0004801)

Where CL:0000066 is ‘epithelial cell’ and UBERON:0004801 is ‘cervix epithelium’

Other examples

1. When a protein both positively and negatively regulates a process/activity under certain conditions, e.g. when bound to something, when located in a particular cell or component, etc.

2. When a protein is located in secretions, such as tears or saliva; currently have no GO terms for these, only 'extracellular space'.

Could add in an extension using Uberon terms, e.g. 'lacrimal gland secretion' or 'saliva'

Where can I get them?

- Download
 - <http://geneontology.org/GO.downloads.annotations.shtml>
 - Groups providing: UniProt, IntAct, MGI, PomBase, DictyBase, AgBase, WormBase
- Search and Browsing
 - Cross-species
 - AmiGO 2 – <http://amigo2.berkeleybop.org>
 - QuickGO (next year) - <http://www.ebi.ac.uk/QuickGO/>
 - MOD interfaces
 - PomBase – <http://pombase.org>

Display of annotation extensions in PomBase

pap1 (SPAC1783.07c)

GO:0036091	positive regulation of transcription from RNA polymerase II promoter in response to oxidative stress	IMP	Castillo EA et al. (2002)	2
	regulates pmd1	IMP	Toone WM et al. (1998)	
	regulates bfr1	IMP	Toone WM et al. (1998)	
	regulates ctt1	IMP	Toone WM et al. (1998)	
	regulates pgr1			97)
	regulates trr1			i. (1998)
	regulates obr1	IMP	Toone WM et al. (1998)	

Independent extensions

GO:0001077	RNA polymerase II core promoter proximal region sequence-specific DNA binding transcription factor activity involved in positive regulation of transcription			26
	regulates sod1	IMP	Mutoh N et al. (2002)	
	regulates gst1	IMP	Kim HG et al. (2004)	
	regulates obr1	IMP	Toda T et al. (1992)	
	during regulation of transcription from RNA polymerase II promoter in response to oxidative stress, regulates hsr1	IMP	Chen D et al. (2008)	
	during regulation of transcription from RNA polymerase II promoter in response to oxidative stress, regulates pof14	IMP	Tafforeau L et al. (2006)	

Conjunctive extension

Note, PomBase has replaced annotation extension relation names with more human-readable versions in their web display

Display of annotation extensions in AmiGO2

Additional Information for transcription factor Pap1/Caf3 (PomBase:SPAC1783.07c)

Associations

Filter: X

Your search is pinned to these filters

+ document_category: annotation

+ bioentity: PomBase:SPAC1783.07c

No current user filters.

▶ Source

▶ Assigned by

▶ Ontology (aspect)

▶ Evidence type

▶ PANTHER family

▶ Taxon

▶ Involved in

▶ Regulates + involved in

Found entities

Total: 37; showing 1 to 10



Gene/Product	Gene/Product name	Annotation	Annotation extension	Source	Taxon	Evidence
pap1	transcription factor Pap1/Caf3	nucleus	exists_during cellular response to hydrogen peroxide	PomBase	Schizosaccharomyces pombe	IDA
pap1	transcription factor Pap1/Caf3	cellular response to caffeine		PomBase	Schizosaccharomyces pombe	IMP
pap1	transcription factor Pap1/Caf3	RNA polymerase II core promoter proximal region sequence-specific DNA binding	has_regulation_target PomBase:SPAC3H1.11 happens_during regulation of transcription from RNA polymerase II promoter in response to oxidative stress	PomBase	Schizosaccharomyces pombe	IMP

Conjunctive extension

Curation tool support

- Supported in
 - Protein2GO (UniProt, DictyBase, WormBase, AgBase, SGD)
 - CANTO (PomBase)
 - MGI curation tool

Curating annotation extensions in Protein2GO

▼ **Add annotation** If you have a large number of annotations to add, that can more easily be submitted via a file upload, please contact goa@ebi.ac.uk

Protein:	Q01663	pap1	Qualifier:		GO ID:	GO:0005634	nucleus	
Evidence:	IDA		Reference:	PUBMED:123124	With:		Interacting Taxon:	
Extension:								

Annotation Extension

▼ Statement Group

Relation subset	Relation	Database Identifier
-----------------	----------	---------------------

(All relations)	(none)	(none)
-----------------	--------	--------

- (All relations)
 - GO:biological_process
 - GO:cellular_component
 - GO:molecular_function
 - cell_or_anatomical
 - chemical
 - developmental_stages
 - sequence_feature
 - sequence_or_complex
- current value.
- dependent_on
 - during
 - exists_during
 - in_absence_of
 - in_presence_of
 - localization_dependent_on
 - modified_by
 - not_dependent_on
 - not_during
 - not_exists_during
 - part_of

atchpad: (empty)

ology in QuickGO

OK Cancel

Curating annotation extensions in Protein2GO

Annotation Extension

Statement Group

Relation subset	Relation	Database	Identifier
cell_or_anatomical	part_of	CL	epith



Add new statement group



Copy to scratchpad



Paste from scratchpad



Show annotation extension relations onto

Current value:

For adding independent extensions

Autocomplete if a relation and identifier type is selected

- 0000074 epithem cell
- 0000066 epitheliocyte
- 0000066 epithelial cell
- 0002150 epithelioid cell
- 0011108 colon epithelial cell
- 0002484 epithelial melanocyte
- 0002150 epithelioid histocyte
- 0002150 epitheloid macrophage
- 0002368 airway epithelial cell
- 0000185 basket epithelial cell
- 0002327 breast epithelial cell
- 0002535 cervix epithelial cell
- 0002150 epithelioid macrophage
- 0002518 kidney epithelial cell

For adding conjunctive extensions

Curating annotation extensions in Protein2GO

Annotation Extension

Statement Group				
Relation subset	Relation	Database	Identifier	
sequence_or_complex	has_direct_input	UniProtKB	Q4VCS5	AMOT (Homo sapiens): Angiomotin
Statement Group				
Relation subset	Relation	Database	Identifier	
sequence_or_complex	has_direct_input	UniProtKB	P12345	GOT2 (Oryctolagus cuniculus): Aspartate aminotransferase, mitochondrial

- + Add new statement group
- Copy to scratchpad Paste from scratchpad: (empty)
- Show annotation_extension relations ontology in QuickGO

Conjunctive extension

Independent extensions

Current value:

has_direct_input(UniProtKB:Q4VCS5)|has_direct_input(UniProtKB:P12345)

OK Cancel

Curating annotation extensions in Protein2GO

Add annotation If you have a large number of annotations to add, that can more easily be submitted via a file upload, please contact goa@ebi.ac.uk

Protein:	Q01663	pap1	Qualifier:		GO ID:	GO:0005634	nucleus	Interacting Taxon:	
Evidence:	IDA		Reference:	PUBMED:123124	With:				
Extension:	part_of(CL:0000066),part_of(UBERON:0000002)								

Source Protein	Symbol	Qualifier	GO	Term	Ev	CC Reference	With	Extension	Int. Tax.	Hstry Cmnts
<input type="checkbox"/> Manual										
Available actions: <input type="button" value="Delete"/> <input type="button" value="Update"/> <input type="button" value="Transfer Annotation(s)..."/> <input type="button" value="Compare GO Terms"/> <input type="button" value="Dispute Annotation(s)..."/> <input type="button" value="View In IntAct"/>										
Process										
<input type="checkbox"/>	SPOM	Q01663	pap1	GO:0006357	regulation of transcription from RNA polymerase II promoter	IMP	PUBMED:22840777	has_regulation_target(PomBa...		

Are annotation extensions useful?

Need to have:

- a larger sample set
- more curators/groups contributing annotation extensions
- GO analysis tool providers to include annotation extensions

GO annotations with extensions can give an improved level of detail and interconnection, supporting more sophisticated querying and analysis

e.g. give me all the human proteins that are involved in blood vessel remodeling during retina vasculature development in the camera-type eye.

e.g. give me all the mouse proteins that have protein kinase activity in kidney cells

A method for increasing expressivity of Gene Ontology annotations using a compositional approach

Resources

- Introduction to annotation extensions:
<http://www.geneontology.org/GO.annotation.extension.shtml>
- Usage examples for each relationship (not complete):
http://wiki.geneontology.org/index.php/Annotation_usage_examples_for_each_annotation_extension_relation
- Interactive graphical visualisation of relationships:
<http://www.ebi.ac.uk/QuickGO/AnnotationExtensionRelations.html>
- OBO Foundry – for finding other ontology IDs, e.g. CL or UBERON:
<http://www.obofoundry.org/>
- Ontology Lookup Service:
<http://www.ebi.ac.uk/ontology-lookup/>
- Annotation Extension Relations OBO file:

http://viewvc.geneontology.org/viewvc/GO-SVN/trunk/ontology/extensions/go_annotation_extension_relations.obo?view=log

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 - Mark McDowell, Kim Rutherford

Reference: *Huntley,R., Harris,M., Alam-Faruque,Y., Blake,J., Carbon,S., Dietze,H., Dimmer,E., Foulger,R., Hill,D., Khodiyar,V., et al. (2014) A method for increasing expressivity of Gene Ontology annotations using a compositional approach. BMC Bioinformatics, 15, 155.*