The Cardiovascular Gene Annotation Initiative: Current and Future Aims

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Project aims

•**Started in November 2007**, the **Cardiovascular Gene Annotation Initiative** is a collaboration between University College London, the European Bioinformatics Institute and King's College London.

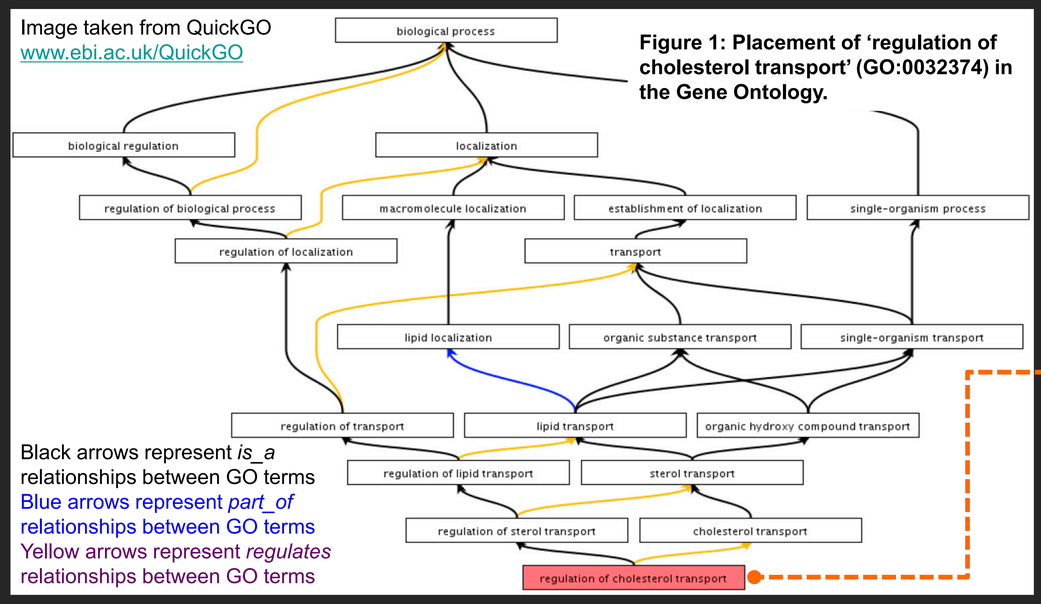
•Funded by the British Heart Foundation our aim is to provide high-quality annotations to the products of genes relevant to cardiovascular processes and disease.

•These annotations are available through the GO and IntAct databases and provide key resources for researchers wishing to understand the biological role of a gene product.

•We will be dividing our time equally between using Gene Ontology (GO) to create microRNA and protein annotations and to capture protein-protein interaction data.

•To create gene annotations we extract data from primary papers, and some reviews. Our main focus is human, but we also capture information from model organisms including rat and mouse..

Image taken from QuickGO
www.ebi.ac.uk/QuickGO



Black arrows represent *is_a* relationships between GO terms
Blue arrows represent *part_of* relationships between GO terms
Yellow arrows represent *regulates* relationships between GO terms

Figure 1: Placement of 'regulation of cholesterol transport' (GO:0032374) in the Gene Ontology.

Anatomy of GO annotation

GO annotation is the practice of capturing information about a gene product using terms from the Gene Ontology. GO contains three structured controlled vocabularies (ontologies) that describe gene products in terms of their associated ***biological processes***, ***subcellular locations*** and ***molecular functions***, in a species-independent manner.

GO terms are assigned to proteins based on different evidence:

IDA = inferred from direct assay
TAS = traceable author statement
IC = inferred by curator

Accession	P06727
Gene	APOA4
Taxonomy	Homo sapiens
Description	Apolipoprotein A-IV

J Clin Invest. 2004 Jul;114(2):260-9.

Apolipoprotein A-IV inhibits experimental colitis.

Vowinkel T[1], Mori M, Krieglstein CF, Russell J, Saijo F, Bharwani S, Turnage RH, Davidson WS, Tso P, Granger DN, Kalogeris TJ.

Abstract

The antiatherogenic properties of apoA-IV suggest that this protein may act as an anti-inflammatory agent. We examined this possibility in a mouse model of acute colitis. Mice consumed 3% dextran sulfate sodium (DSS) in their drinking water for 7 days, with or without daily intraperitoneal injections of recombinant human apoA-IV. apoA-IV significantly and specifically delayed the onset, and reduced the severity and extent of, DSS-induced inflammation, as assessed by clinical disease activity score, macroscopic appearance and histology of the colon, and tissue myeloperoxidase activity. Intravital fluorescence microscopy of colonic microvasculature revealed that apoA-IV significantly inhibited DSS-induced leukocyte and platelet adhesive interactions. Furthermore, apoA-IV dramatically reduced the upregulation of P-selectin on colonic endothelium during DSS-colitis. apoA-IV knockout mice exhibited a significantly greater inflammatory response to DSS than did their WT littermates; this greater susceptibility to DSS-induced inflammation was reversed upon exogenous administration of apoA-IV to knockout mice. These results provide the first direct support for the hypothesis that apoA-IV is an endogenous anti-inflammatory protein. This anti-inflammatory effect likely involves the inhibition of P-selectin-mediated leukocyte and platelet adhesive interactions.

Each annotation is attached to a reference for traceability.

GO Term Name	Evidence	Reference	With	Assigned By
Process				
retinoid metabolic process	TAS	Reactome:REACT_24968		Reactome
innate immune response in mucosa	IDA	PMID:15254593		BHF-UCL
lipid transport	IDA	PMID:1935934		BHF-UCL
lipid transport	IDA	PMID:3095477		BHF-UCL
leukocyte cell-cell adhesion	IDA	PMID:15254593		BHF-UCL
phototransduction, visible light	TAS	Reactome:REACT_160125		Reactome
cholesterol metabolic process	IDA	PMID:1935934		BHF-UCL
positive regulation of cholesterol esterification	IDA	PMID:1935934		BHF-UCL
positive regulation of triglyceride catabolic process	IDA	PMID:2307668	BHF-UCL denotes	BHF-UCL
regulation of cholesterol transport	IDA	PMID:11940599	GO terms assigned	BHF-UCL
cholesterol efflux	IDA	PMID:11162594	by this project	BHF-UCL
cholesterol efflux	IDA	PMID:1935934		BHF-UCL
phospholipid efflux	IDA	PMID:11162594		BHF-UCL
chylomicron remodeling	IC	PMID:2307668	GO:0051006	BHF-UCL

ID	GO:0034371
Name	chylomicron remodeling
Ontology	Biological Process
Definition	The acquisition, loss or modification of a protein or lipid within a chylomicron, including the hydrolysis of triglyceride by lipoprotein lipase and the subsequent loss of free fatty acid.

Each GO term has a unique ID, name and definition. A GO term may also contain one or more synonyms to aid searching.

Figure 2: Anatomy of an annotation: a subset of biological process GO annotations for human APOA4. Displayed in the EBI GO browser (www.ebi.ac.uk/QuickGO).

GO annotation of microRNAs

Direct curation of the roles of miRNAs is expected to improve miRNA functional analysis that has so far relied on indirect analysis of the gene targets' functions

- The aims of the microRNA project are to:
  (i) draw up guidelines for consistent literature-based annotation of miRNAs in consultation with the GO Consortium
  (ii) curate miRNAs that are involved with cardiovascular development and related processes
  (iii) capture the targets of the cardiovascular-related miRNAs
- The guidelines are currently in progress and due to go to the GO Consortium for review
- We have also annotated the roles of the key human proteins, e.g. DICER, DROSHA, in the miRNA processing pathway using experimental evidence from published papers
- Our first priorities for curation are miRNAs involved in cardiac conduction, including miR-1, miR-133 and miR-208a
- The miRNA annotations are available in the regular GO annotation files; these will soon be available in AmiGO2 and the new version of QuickGO.

Gene/product	Gene/product name	Qualifier	Direct annotation	Annotation extension	Source	Taxon	Evidence	Evidence with	PANTHER family	Isoform	Reference
URS000024463E	hsa-miR-29b-3p		negative regulation of transforming growth factor beta receptor signaling pathway	occurs_in CL:0002539	BHF-UCL	Homo sapiens	IGI	UniProtKB:P01137			PMID:22269326
URS0000346F1C	hsa-miR-200c-5p		gene silencing by miRNA	has_direct_input ENST00000320985	BHF-UCL	Homo sapiens	IDA				PMID:23938772
AGO2	protein argonaute-2		miRNA loading onto RISC involved in gene silencing by miRNA		BHF-UCL	Homo sapiens	IDA		eukaryotic translation initiation factor 2c pthr22891		PMID:18178619

Figure 3: Annotation of miRNAs and miRNA processes. AmiGO2 view of BHF-UCL annotations. CL:0002539 is the Cell Ontology ID for aortic smooth muscle cell; ENST00000320985 is the Ensembl ID for a *ZEB1* transcript.

Capture of protein-protein interactions

- During the past year we have submitted 1158 protein-protein interactions (PPIs) to IntAct, from the curation of 130 papers.
- Currently in IntAct there are 2075 PPIs associated with the proteins encoded by the genes adjacent to the 88 genetic loci associated with HDL levels (Asselbergs *et al.* 2013), 5% of these were submitted by the BHF supported curators.
- These additional PPIs have substantially improved the networks available for some proteins, for example our annotations have increased the number of PPIs associated with ABCA1 by 40%, from 14 PPIs to 20 PPIs.

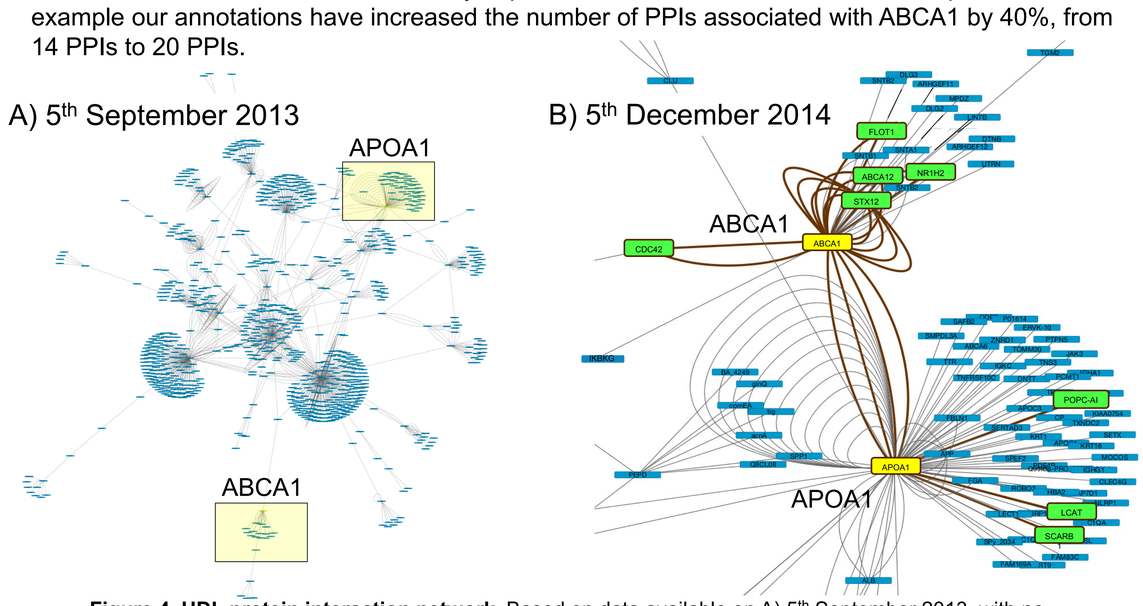


Figure 4. HDL protein interaction network. Based on data available on A) 5th September 2013, with no interactions between APOA1 and ABCA1 (yellow nodes) compared to B) enlarged view of part of network available on 5th December 2014, with interaction between APOA1 and ABCA1 included due to interactions submitted by the BHF-UCL curators (brown edges). LCAT BHF-UCL submitted interactors.

References and further reading

- **Ten quick tips for using the Gene Ontology**. Blake J.A. PLoS Comput Biol. Nov;9(11):e1003343 (2013). *PMID 24244145.*
- **The Gene Ontology: enhancements for 2011**. The Gene Ontology Consortium. Nucleic Acids Res. 40, D559-564 (2012). *PMID 22102568.*
- **The IntAct molecular interaction database in 2012**. Kerrien S. *et al*. Nucleic Acids Res. 40, D841-846 (2012). *PMID 22121220.*
- **Progress in genetic association studies of plasma lipids**. Asselbergs, F.W., Lovering, R.C., Drenos, F. *Curr Opin Lipidol, 24 (2)*, 123-128 (2013). *PMID:23385652.*
- **The impact of focused Gene Ontology curation of specific mammalian systems**. Alam-Faruque, Y. *et al*. *PLoS One, 6 (12)*, e27541. (2011). *PMID:22174742.*
- **The representation of heart development in the Gene Ontology**. Khodiyar, V. K. *et al. Dev Biol, 354 (1)*, 9-17. (2011) *PMID:21419760.*

How YOU can help

- We are keen to hear from you about the genes and processes **YOU** think we should be annotating. Please speak to us, or email **r.lovering@ucl.ac.uk**.
- Search the GO annotations associated with your favourite gene - let us know if you think any annotations are missing.
- Send us your cardiovascular-relevant papers to be annotated.
- To follow our progress, please ask to be added to our quarterly newsletter, or visit our project at www.ucl.ac.uk/functional-gene-annotation/cardiovascular.

www.ucl.ac.uk/functional-gene-annotation/cardiovascular
www.ebi.ac.uk/intact
www.ebi.ac.uk/GOA
www.geneontology.org

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