

Phylogenetics

iHam and pyHam: visualizing and processing hierarchical orthologous groups

Clément-Marie Train^{1,2,3}, Miguel Pignatelli^{4,5}, Adrian Altenhoff^{1,2} and Christophe Dessimoz^{1,3,6,7,8,*} 

¹SIB Swiss Institute of Bioinformatics, 1015 Lausanne, Switzerland, ²ETH Zurich, Department of Computer Science, 8092 Zurich, Switzerland, ³Center for Integrative Genomics, University of Lausanne, 1015 Lausanne, Switzerland, ⁴Open Targets and ⁵EMBL-European Bioinformatics Institute, Wellcome Genome Campus, Hinxton, Cambridge CB10 1SD, UK, ⁶Department of Computational Biology, University of Lausanne, 1015 Lausanne, Switzerland, ⁷Department of Genetics, Evolution and Environment, University College London, London WC1E, UK and ⁸Department of Computer Science, University College London, London WC1E 6BT, UK

*To whom correspondence should be addressed.

Associate Editor: Russell Schwartz

Received on May 9, 2018; revised on November 24, 2018; editorial decision on November 28, 2018; accepted on November 30, 2018

Abstract

Summary: The evolutionary history of gene families can be complex due to duplications and losses. This complexity is compounded by the large number of genomes simultaneously considered in contemporary comparative genomic analyses. As provided by several orthology databases, hierarchical orthologous groups (HOGs) are sets of genes that are inferred to have descended from a common ancestral gene within a species clade. This implies that the set of HOGs defined for a particular clade correspond to the ancestral genes found in its last common ancestor. Furthermore, by keeping track of HOG composition along the species tree, it is possible to infer the emergence, duplications and losses of genes within a gene family of interest. However, the lack of tools to manipulate and analyse HOGs has made it difficult to extract, display and interpret this type of information. To address this, we introduce interactive HOG analysis method, an interactive JavaScript widget to visualize and explore gene family history encoded in HOGs and python HOG analysis method, a python library for programmatic processing of genes families. These complementary open source tools greatly ease adoption of HOGs as a scalable and interpretable concept to relate genes across multiple species.

Availability and implementation: iHam's code is available at <https://github.com/DessimozLab/iHam> or can be loaded dynamically. pyHam's code is available at <https://github.com/DessimozLab/pyHam> and or via the pip package 'pyham'.

Contact: christophe.dessimoz@unil.ch

1 Introduction

The evolution of a gene family describes the history of all the genes that shared a common ancestral gene. Those genes called homologs can be distinguished into orthologs if they start diverging by speciation and paralogs if they start diverging by duplication (Fitch, 1970). In comparative genomics, gene families are a fundamental resource

since they tend to represent the links between several organisms from a gene centric perspective and allow us to understand how genes and genomes have evolved over time.

The evolutionary history of gene families can be studied by visualizing reconciled gene trees, using web-based resources such as Ensembl (Herrero *et al.*, 2016), HOGENOM/HOVRGEN (Dufayard *et al.*,

Table 1. Support for iHam and pyHam by various HOG inference resources

Resource	Species tree format	OrthoXML	iHam Support	pyHam Support				
OMA browser	PhyloXML and Newick	All HOGs, or one HOG at a time	YES	YES				
OMA standalone	PhyloXML and Newick	All HOGs	YES	YES				
Ensembl	Newick	One HOG at a time	YES </tr <tr> <td>HieranoidDB</td> <td>Newick</td> <td>One HOG at a time</td> <td>YES</td> <td>YES</td> </tr>	HieranoidDB	Newick	One HOG at a time	YES	YES
HieranoidDB	Newick	One HOG at a time	YES	YES				

2005), EggNOG (Huerta-Cepas *et al.*, 2016), PhylomeDB (Huerta-Cepas *et al.*, 2014) or tools such as ETE (Huerta-Cepas *et al.*, 2010) and SylvX (Chevenet *et al.*, 2016). However, when considering large families across many species, reconciled gene trees can become prohibitively complex to infer and interpret.

As a scalable alternative to reconciled gene trees, the concept of Hierarchical Orthologous Groups (HOGs) is increasingly adopted. HOGs generalize Fitch's definition of orthology to more than two species, by grouping sequences that have descended from a common ancestral gene within a clade of interest. Thus, the set of all HOGs defined for a given clade corresponds to the set of ancestral genes in the common ancestor of that clade. Furthermore, if HOGs are available for nested clades (e.g. vertebrates versus mammals), the difference between their HOG repertoires imply gene duplication and loss events on the branch separating them: a HOG split implies a duplication, while a HOG disappearance implies a loss.

HOGs are inferred by several leading orthology databases such as OrthoDB (Zdobnov *et al.*, 2017), EggNOG (Huerta-Cepas *et al.*, 2016), HieranoidDB (Kaduk *et al.*, 2017) or OMA (Altenhoff *et al.*, 2018). In OMA, for instance, some HOGs connect large gene families of over 100 000 members across 1000's of genomes. Because of this complexity, manual exploration of gene families encoded in HOGs can be challenging. As of now, there is a lack of tool for visualizing, exploring and processing HOGs to tackle specific biological questions.

In this application note, we introduce two tools to facilitate the visualization and analysis of HOGs: interactive HOG analysis method (iHam) for web-based interactive visualization and exploration of individual HOGs and python HOG analysis method (pyHam) to perform aggregate analyses.

2 iHam

iHam is an interactive JavaScript tool to visualize the evolutionary history of a specific gene family encoded in HOGs. The viewer is composed of two panels (Fig. 1A): a species tree which lets the user select a node to focus on a particular taxonomic range of interest, and a matrix that organizes extant genes according to their membership in species (rows) and HOGs (columns). The tree-guided matrix representation of HOGs facilitates: (i) to delineate orthologous groups at given taxonomic ranges, (ii) to infer duplication and loss events in the species tree, (iii) gauge the cumulative effect of duplications and losses on gene repertoires and (iv) to identify potential mistakes in genome assembly, annotation or orthology inference (e.g. if losses are concentrated on terminal branches—suggestive of incomplete genomes; or if the species coverage within a HOG looks implausible—suggestive of orthology inference error).

Users can customize the view in different ways. They can color genes according to protein length or GC-content. Low-confidence HOGs can be masked. Irrelevant species clades can be collapsed. iHam is a reusable web widget that can be easily embedded into a website; for instance, it is used to display HOGs in OMA (<http://omabrowser.org>; Altenhoff *et al.*, 2018). Implemented as a

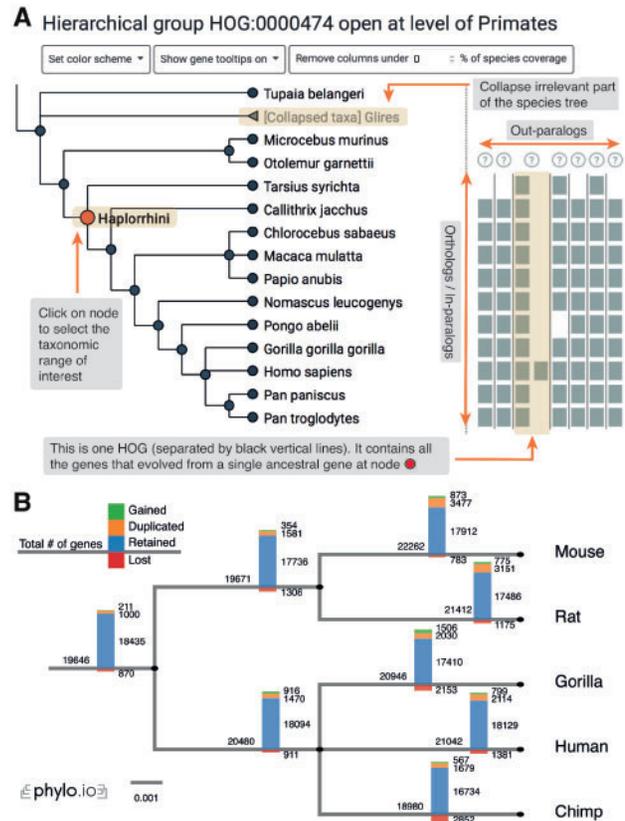


Fig. 1. (A) iHam. An excerpt of the Tetraspanin family at the Haplorrhini level: the tree depicts relationships between species, squares depict genes and HOGs are delineated by vertical bars. (B) pyHam can be used to map gene losses, duplications or new appearances ('gained') onto species trees (here, using the NCBI taxonomy tree)

JavaScript library using the TnT framework (Pignatelli, 2016), iHam merely requires as input HOGs in the standard OrthoXML format (Schmitt *et al.*, 2011) and the underlying species tree in newick or PhyloXML format (supported resources listed in Table 1).

3 pyHam

pyHam makes it possible to extract useful information from HOGs encoded in standard OrthoXML format. It is available both as a python library and as a set of command-line scripts. Input HOGs in OrthoXML format are available from multiple bioinformatics resources, including OMA, Ensembl and HieranoidDB (Table 1).

The main features of pyHam are: (i) given a clade of interest, extract all the relevant HOGs, each of which ideally corresponds to a distinct ancestral gene in the last common ancestor of the clade; (ii) given a branch on the species tree, report the HOGs that duplicated on the branch, got lost on the branch, first appeared on that branch

or were simply retained; (iii) repeat the previous point along the entire species tree and plot an overview of the gene evolution dynamics along the tree (Fig. 1B) and (iv) given a set of nested HOGs for a specific gene family of interest, generate a local iHam web page to visualize its evolutionary history.

4 Conclusion

The combination of iHam and pyHam enable users to unlock the full potential of HOGs.

Acknowledgements

The authors thank Matthieu Muffato and Maria J. Martin for helpful suggestions on early iHam prototypes, and Panu Artimo for implementing the histogram view in *phylo.io* to display pyHam results along species trees. They also thank three anonymous reviewers for helpful comments on early drafts of the manuscript.

Funding

This work was supported by the Swiss National Science Foundation grant 150654, UK BBSRC grant BB/M015009/1 and the Swiss State Secretariat for Education, Research and Innovation (SERI).

Conflict of Interest: none declared.

References

Altenhoff, A.M. *et al.* (2018) The OMA orthology database in 2018: retrieving evolutionary relationships among all domains of life through richer web and programmatic interfaces. *Nucleic Acids Res.*, **46**, D477–D485.

- Chevenet, F. *et al.* (2016) Berry SylvX: a viewer for phylogenetic tree reconciliations. *Bioinformatics*, **32**, 608–610.
- Dufayard, J.-F. *et al.* (2005) Tree pattern matching in phylogenetic trees: automatic search for orthologs or paralogs in homologous gene sequence databases. *Bioinformatics*, **21**, 2596–2603.
- Fitch, W.M. (1970) Distinguishing homologous from analogous proteins. *Syst. Zool.*, **19**, 99–113.
- Herrero, J. *et al.* (2016) Ensembl comparative genomics resources. *Database*, doi: 10.1093/database/bav096.
- Huerta-Cepas, J. *et al.* (2010) ETE: a python environment for tree exploration. *BMC Bioinformatics*, **11**, 24.
- Huerta-Cepas, J. *et al.* (2016) eggNOG 4.5: a hierarchical orthology framework with improved functional annotations for eukaryotic, prokaryotic and viral sequences. *Nucleic Acids Res.*, **44**, D286–D293.
- Huerta-Cepas, J. *et al.* (2014) PhylomeDB v4: zooming into the plurality of evolutionary histories of a genome. *Nucleic Acids Res.*, **42**, D897–D902.
- Kaduk, M. *et al.* (2017) HieranoiDB: a database of orthologs inferred by hieranoid. *Nucleic Acids Res.*, **45**, D687–D690.
- Pignatelli, M. (2016) TnT: a set of libraries for visualizing trees and track-based annotations for the web. *Bioinformatics*, **32**, 2524–2525.
- Schmitt, T. *et al.* (2011) Letter to the editor: seqXML and OrthoXML: standards for sequence and orthology information. *Brief. Bioinform.*, **12**, 485–488.
- Zdobnov, E. *et al.* (2017) OrthoDB v9.1: cataloging evolutionary and functional annotations for animal, fungal, plant, archaeal, bacterial and viral orthologs. *Nucleic Acids Res.*, **45**, D744–D749.