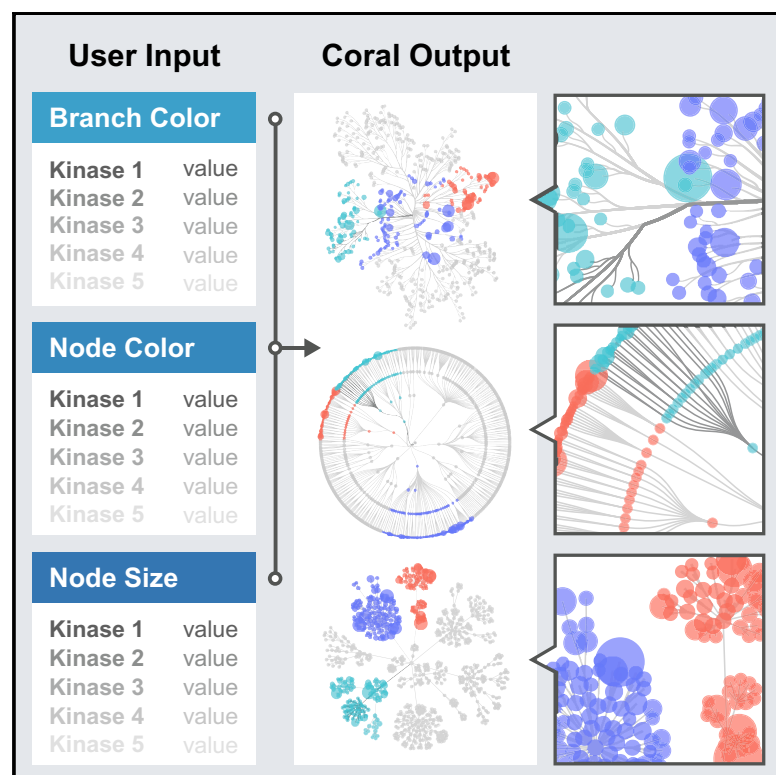


# Cell Systems

## Coral: Clear and Customizable Visualization of Human Kinome Data

### Graphical Abstract



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### In Brief

Coral is a user-friendly web application that produces highly customizable, publication-quality visualizations of human kinome data. Users can encode qualitative and quantitative data in the branches and nodes of the kinome network and choose between multiple layouts. Coral has broad utility for communicating genomic, proteomic, and kinase profiling results.

### Highlights

- Coral is a user-friendly web application for the visualization of human kinome data
- Qualitative and quantitative data can be encoded in edge and node color and node size
- Users can visualize the kinome in multiple forms, including tree and network views
- Coral generates high-resolution vector figures fit for direct use in publications



# Coral: Clear and Customizable Visualization of Human Kinome Data

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## SUMMARY

Protein kinases represent one of the largest gene families in eukaryotes and play roles in a wide range of cell signaling processes and human diseases. Current tools for visualizing kinase data in the context of the human kinome superfamily are limited to encoding data through the addition of nodes to a low-resolution image of the kinome tree. We present Coral, a user-friendly interactive web application for visualizing both quantitative and qualitative data. Unlike previous tools, Coral can encode data in three features (node color, node size, and branch color), allows three modes of kinome visualization (the traditional kinome tree as well as radial and dynamic force networks), and generates high-resolution scalable vector graphics files suitable for publication without the need for refinement using graphics editing software. Due to its user-friendly, interactive, and highly customizable design, Coral is broadly applicable to high-throughput studies of the human kinome. The source code and web application are available at [github.com/dphansti/CORAL](https://github.com/dphansti/CORAL) and [phanstiel-lab.med.unc.edu/Coral](https://phanstiel-lab.med.unc.edu/Coral), respectively.

## INTRODUCTION

The human kinome consists of over 500 different protein kinases, which regulate a broad range of cellular processes via substrate phosphorylation. These proteins have been implicated in a variety of diseases, including pathological hypertrophy (Heineke and Molkentin, 2006; Vlahos et al., 2003), rheumatoid arthritis (Gaestel et al., 2009; Patterson et al., 2014), and cancer (Fleuren et al., 2016; Ventura and Nebreda, 2006). As a result, protein kinases are common candidates for drug targets and increasingly the

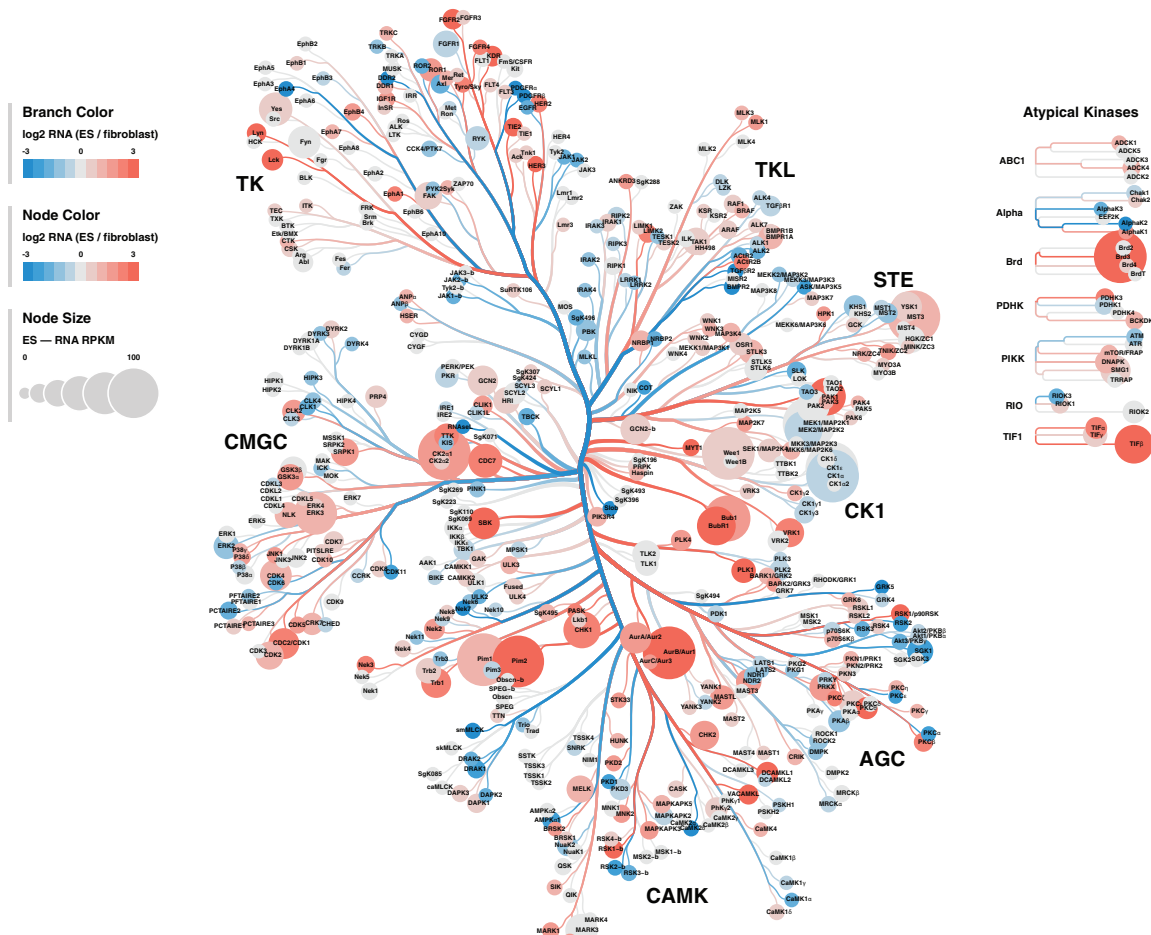
focus of large-scale studies (Cohen, 2002; Cohen and Alessi, 2013; Duong-Ly and Peterson, 2013; Hu et al., 2017; Li et al., 2016; Wu et al., 2016). High-throughput approaches to study kinase abundance and activity—including proteomics, genomics, and kinase profiling screens—have created a need to visualize and interpret results in the greater context of the human kinome.

Multiple paradigms have been established for representing kinome attributes. In 2002, Manning et al. generated a kinome map based on the sequence similarity between publicly available and predicted protein kinase domains and categorized the 518 known human kinases into nine superfamilies (Manning et al., 2002). This dendrogram was then modified with reference to other trees and manually refined into an aesthetically pleasing image in which branches are colored by kinase group, and kinase names are HTML links to websites with information specific to each kinase ([www.cellsignal.com](http://www.cellsignal.com)). Several groups have manually modified this image, encoding qualitative or quantitative kinase information in either branch color (Fleuren et al., 2016; Phanstiel et al., 2011) or the color and size of circular nodes placed at the end of each branch (Hu et al., 2017; Li et al., 2016; Wu et al., 2016). These figures are powerful tools for data interpretation and communication but are labor intensive to create and often infeasible for large or more complex experimental datasets. To address this issue, several programs have been developed to automate kinome visualization, including Kinome Render (Chartier et al., 2013), the NCGC Kinome Viewer ([tripod.nih.gov](http://tripod.nih.gov)), and KinMap (Eid et al., 2017), which have been widely adopted by the kinase research community. Because these existing methods encode information solely by adding nodes to the existing image created by Cell Signaling Technology, they suffer from three limitations: (1) they offer no ability to recolor kinase branches either for aesthetic purposes or to encode information, (2) they only feature a single paradigm for kinome representation, the semi-quantitative tree, and (3) they produce low-resolution images that are not well suited for publication.

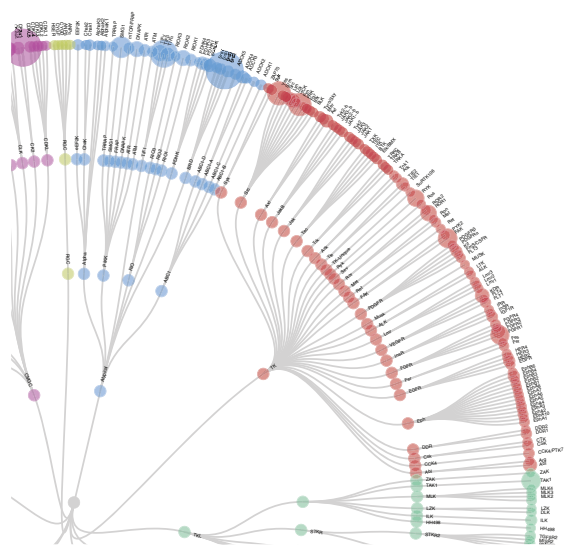
Here, we describe Coral, an interactive web application for kinome annotation, which allows encoding of qualitative and quantitative kinase attributes in branch color, node color, and



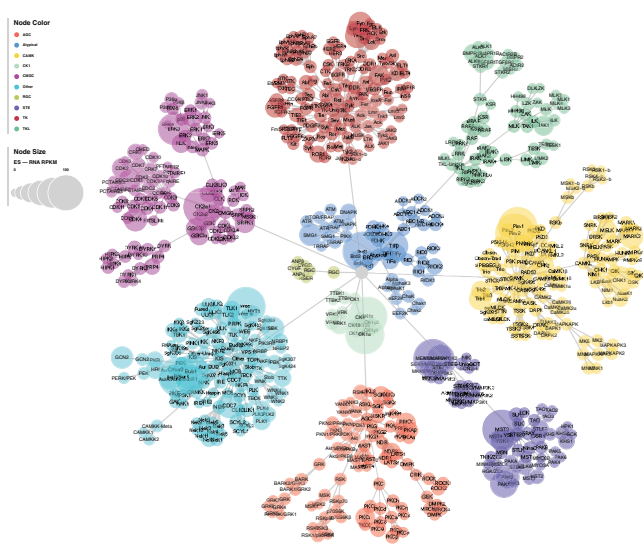
A



B



C



**Figure 1. Three Modes of Kinome Visualization**

For a Figure360 author presentation of Figure 1, see <https://doi.org/10.1016/j.cels.2018.07.001>.

- (A) A “Tree” plot generated by Coral in which log<sub>2</sub>-fold change for RNA is encoded in branch color and node color, and RNA RPKM values are encoded in node size.  
(B) A zoomed-in image of a “Circle” plot generated by Coral that depicts kinase group in node color and RNA RPKM values in node size.  
(C) A “Force” plot generated by Coral depicting the same data as in (B).

node size. Coral offers multiple modes of kinome visualization, including the traditional kinome tree, as well as interactive static and dynamic network layouts enabled by the D3 javascript library. Importantly, the images produced by Coral are highly customizable and can be downloaded as high-resolution, publication-quality vector images. Coral was designed to be user friendly and includes example data, extensive documentation, and example outputs for all features.

## RESULTS

Coral is a highly customizable kinome visualization tool that provides unprecedented flexibility in terms of attribute encoding and visualization modalities, allowing for the creation of high-resolution figures through a user-friendly platform.

Coral offers multiple modes of data input and supports a variety of kinase identifiers. The user can supply both qualitative and quantitative data by selecting from pre-populated pull-down menus or by pasting information from common data sources such as spreadsheet editors. Coral inputs and outputs are compatible with multiple identifiers including UniProt, ENSEMBL, Entrez, and HGNC, as well as an alphanumeric version of the names displayed in the original kinome tree, referred to as their CoralID.

Data can be encoded in branch color, node color, node size, and any combination thereof. Coral supports categorical, sequential, and divergent color schemes by providing several color-blind-friendly palettes, as well as the option to create your own. This allows for a straightforward incorporation of multiple types of data within a single figure, using intuitive color schemes and automatically generated legends for ease of interpretation.

Coral features three modalities of visualization. First, through the use of a newly rendered scalable vector graphics (SVG) file, Coral outputs high-resolution images with data encoded in a kinome tree based on the one created by Cell Signaling Technology (Figure 1A). Second, data can be depicted in a circular radial kinase network with nodes for kinases, groups, families, and sub-families (Figure 1B). Finally, kinase attributes can be displayed in a dynamic force-directed network that uses the same underlying network structure as the circle plot (Figure 1C). All plots can be downloaded as high-resolution vector graphics files suitable for publication without the need for further refinement in graphics editing software. In addition, Coral provides advanced options for customizing features, including titles, legends, fonts, transparencies, and node highlights. Users can also browse a searchable and sortable table of kinases and their associated attributes.

Coral was designed with user experience in mind. Each plot responds to user input, updates in real time, and features drag and zoom capabilities. Individual nodes are also interactive and either include links to UNIPROT pages or expand when hovered over, making it easier to read text and visualize colors for individual nodes. Features are extensively documented in the Coral information pages, which include both example data and example outputs for each feature to help familiarize users with its many options.

## DISCUSSION

Due to its flexibility and wealth of customizable features, Coral can potentially be applied to many areas of study within human

kinome research. Quantitative data can be presented through branch color, node color, and node sizes and can feature sequential information (e.g., transcript or protein levels, kinase activity, or  $-\log p$  values) as well as divergent values (e.g.,  $\log_2$ -fold change). Qualitative data such as built-in kinase family assignments can easily differentiate between different classes of kinases and can also be applied to highlight kinases of interest such as targets of kinase inhibitors.

The traditional and network kinome structures can be used to highlight different features of data depending on the application. For example, the Tree layout may be useful for sharing data among audiences familiar with the historically used phylogenetic tree, while the network layouts are useful when there is a need to explicitly include family and subfamily delineations and highlight the hierarchy of the kinase classifications.

With the constantly growing wealth of human kinase studies, Coral fills a need for easily generated, customizable, high-resolution images for the intuitive visualization of kinase data in the broader context of the human kinome.

## STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- CONTACT FOR REAGENT AND RESOURCE SHARING
- METHOD DETAILS
- DATA AND SOFTWARE AVAILABILITY

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## AUTHOR CONTRIBUTIONS

Conceptualization, D.H.P.; Software, D.H.P., E.M.D., M.E.B., B.A.A., I.J.R., and K.S.M.; Writing, K.S.M. and D.H.P.; Visualization, E.M.D.; Supervision, D.H.P.; Resources, D.H.P., S.M.G., and J.H.

## DECLARATION OF INTERESTS

The authors declare no competing interests.

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## WEB RESOURCES

Cell Signaling Technology (CST), Antibodies, Reagents, Proteomics, Kits and Consumables, [www.cellsignal.com](http://www.cellsignal.com).

Coral Source Code, [github.com/dphansti/CORAL](https://github.com/dphansti/CORAL).

Coral, [phanstiel-lab.med.unc.edu/Coral](http://phanstiel-lab.med.unc.edu/Coral).

Tripod Development, Cheminformatics Proving Ground, [tripod.nih.gov](http://tripod.nih.gov).

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## STAR★METHODS

### KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and Algorithms		
R shiny package	Chang et al., 2017	<a href="https://cran.r-project.org/web/packages/shiny/index.html">https://cran.r-project.org/web/packages/shiny/index.html</a>
R shinydashboard package	Chang and Ribeiro, 2017	<a href="https://cran.r-project.org/web/packages/shinydashboard/">https://cran.r-project.org/web/packages/shinydashboard/</a>
R shinyBS package	Bailey, 2015	<a href="https://cran.r-project.org/web/packages/shinyBS/">https://cran.r-project.org/web/packages/shinyBS/</a>
R shinyWidgets package	Perrier and Meyer, 2018	<a href="https://cran.r-project.org/web/packages/shinyWidgets/">https://cran.r-project.org/web/packages/shinyWidgets/</a>
R readr package	Wickham et al., 2017	<a href="https://cran.r-project.org/web/packages/readr/">https://cran.r-project.org/web/packages/readr/</a>
R rsvg package	Ooms, 2017	<a href="https://cran.r-project.org/web/packages/rsvg/">https://cran.r-project.org/web/packages/rsvg/</a>
R RColorBrewer package	Neuwirth, 2014	<a href="https://cran.r-project.org/web/packages/RColorBrewer/">https://cran.r-project.org/web/packages/RColorBrewer/</a>
D3.js javascript library	Bostock et al., 2011	<a href="https://d3js.org/">https://d3js.org/</a>

### CONTACT FOR REAGENT AND RESOURCE SHARING

Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact, Douglas Phanstiel ([douglas\\_phanstiel@med.unc.edu](mailto:douglas_phanstiel@med.unc.edu)).

### METHOD DETAILS

Coral was developed using R and Javascript.

The R package shiny (Chang et al., 2017) and its extensions shinydashboard (Chang and Ribeiro, 2017), shinyBS (Bailey, 2015) and shinyWidgets (Perrier and Meyer, 2018) were used for the web framework.

The R packages readr (Wickham et al., 2017) and rsvg (Ooms, 2017) were used for data manipulation and rendering the SVG elements.

RColorBrewer (Neuwirth, 2014) was utilized for color palettes.

The Circle and Force layouts were written using the D3.js library (Bostock et al., 2011).

The kinome tree was obtained courtesy of Cell Signaling Technology Inc. ([www.cellsignal.com](http://www.cellsignal.com)), and manually redrawn using vector graphics in Adobe Illustrator.

### DATA AND SOFTWARE AVAILABILITY

The Coral web application is available at <http://phanstiel-lab.med.unc.edu/CORAL/>. Source code is available at <https://github.com/dphansti/CORAL>.