Bioinformatics, 35(20), 2019, 4179–4180
doi: 10.1093/bioinformatics/btz179
Advance Access Publication Date: 13 March 2019
Applications Note

OXFORD

Genetics and population analysis

PleioNet: a web-based visualization tool for exploring pleiotropy across complex traits

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Associate Editor: Alfonso Valencia

Received on August 16, 2018; revised on February 20, 2019; editorial decision on March 9, 2019; accepted on March 12, 2019

Abstract

Summary: Pleiotropy plays an important role in furthering our understanding of the shared genetic architecture of different human diseases and traits. However, exploring and visualizing pleiotropic information with currently publicly available tools is limiting and challenging. To aid researchers in constructing and digesting pleiotropic networks, we present PleioNet, a web-based visualization tool for exploring this information across human diseases and traits. This program provides an intuitive and interactive web interface that seamlessly integrates large database queries with visualizations that enable users to quickly explore complex high-dimensional pleiotropic information. PleioNet works on all modern computer and mobile web browsers, making pleiotropic information readily available to a broad range of researchers and clinicians with diverse technical backgrounds. We expect that PleioNet will be an important tool for studying the underlying pleiotropic connections among human diseases and traits.

Availability and implementation: PleioNet is hosted on Google cloud and freely available at http://www.pleionet.com/.

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1 Introduction

Pleiotropy refers to the phenomenon that a gene or genetic variant affects two or more seemingly unrelated phenotypic traits (Solovieff *et al.*, 2013). Pleiotropy was first introduced in the scientific literature more than 100 years ago (Stearns, 2010). Since then, it has played an important role in furthering our understanding of biology and disease. Recent advances in human genomics indicate that pleiotropy is ubiquitous (Chesmore *et al.*, 2018; Visscher and Yang, 2016). The characterization of these pleiotropic mechanisms not only helps explain the shared genetic architecture of different diseases and traits, but also contributes to novel insights in medical genetics and drug development. A greater understanding of the underlying pleiotropic connections inevitably contributes to improving disease classification and treatment and more broadly, precision medicine (Oberg *et al.*, 2016; Solovieff *et al.*, 2013).

Pleiotropy can be dissected using the genotype-phenotype relationship found in genome-wide association studies (GWASs) (Pickrell *et al.*, 2016; Sivakumaran *et al.*, 2011; Solovieff *et al.*, 2013). Findings from these studies are collected in the GWAS catalog, which is a database of all published GWASs maintained by NHGRI and EMBI-EBI (MacArthur *et al.*, 2017). Despite the vast accumulation of genetic information that makes the study of pleiotropy feasible, discovering hidden pleiotropic connections and visualizing their high-dimensional relationships remains challenging and time-consuming, especially when trying to explore many genes and genetic markers in numerous diseases and traits simultaneously. There are 75 977 records with 21 540 mapped genes and 2488 mapped traits in the GWAS catalog (July 2018 version). Interactive web-based visualization that is built on the vast amount of GWAS evidence is crucial to exploring these rich GWAS results to reveal

hidden cross-phenotype relationships and generate clinically meaningful hypotheses. To address these challenges in the exploration of pleiotropy, we developed PleioNet so that users can rapidly construct and digest a specific pleiotropic network of human diseases and traits. It shows complex cross-phenotype relationships in an intuitive and user-friendly network and using it is as simple as browsing a website.

2 Approach

PleioNet is hosted on Google cloud. It has an intuitive and interactive web interface that seamlessly integrates database query and visualization that enables users to quickly explore complex pleiotropic information hidden in the GWAS findings. Figure 1 shows an example interface.

PleioNet consists of three major components. The first component involves choosing which level of specificity in the pleiotropic network. PleioNet has four different levels to choose from, including single nucleotide polymorphisms (SNPs), genes, diseases/traits, and parent terms (ontology categories), each of which is identified in the network with a color-coded node specifying that level. The second component involves the selection of specific genes, genetic markers, and diseases/traits that the user is interested in investigating. PleioNet has the full collection of genes and diseases/traits from the GWAS catalog database to choose from, located in two scroll-down input fields to the left of the network. Select the genes and traits by scrolling through and choosing the option(s) of interest. The user may also type the topic, with the help of autocompletion, into the input field and pick out the desired genes or diseases/traits. The pleiotropic network figure is then generated based on the SNP → Gene → Disease/Trait → Parent Term hierarchical structure. The third major component consists of the plot and summary tabs. The plot tab displays the color-coded pleiotropic network composed of nodes designated by the user. The plotted network can be maneuvered in a number of ways, such as highlighting a specific node and its connections or by zooming in and out. The summary tab details the SNPs and mapped genes and traits depicted in the pleiotropic network in an easily searchable and sortable fashion. PleioNet works on all modern computer and mobile web browsers, making pleiotropic information readily available to a broad range of researchers and clinicians with diverse technical backgrounds. No command line or programing knowledge is necessary to explore this high-dimensional data.

Due to the complexity of pleiotropy and the large database query needed, intuitive visualization combined with convenient query are indispensable to researchers exploring the abundance of pleiotropic information. PleioNet is an efficient visualization tool that helps users digest pleiotropic information and aids in the generation of new hypotheses about gene functions and new treatment strategies as suggested by molecular relationships. Although we focus on human diseases and traits here, PleioNet can easily be extended to non-human genetic studies as well. With an increasing number of GWASs being conducted, the GWAS catalog database will become even more comprehensive and enable the inclusion of more pleiotropic relationships. Ultimately, PleioNet may serve to connect all complex traits.

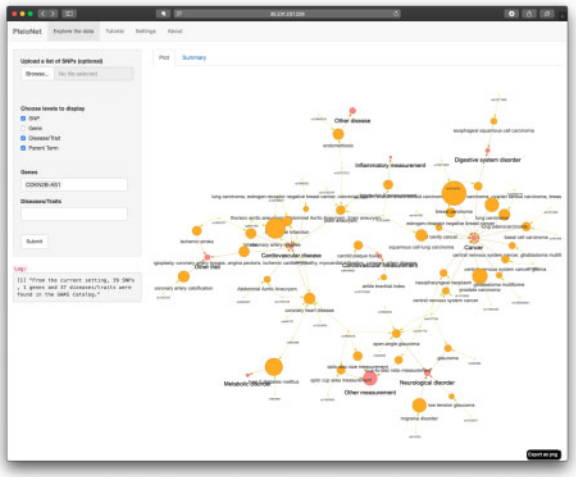

Fig. 1. Web interface of PleioNet On the left panel, users can choose the levels, i.e. SNP, gene, disease/trait and parent term (ontology categories), to display and customize the genes and diseases/traits that they are interested in observing. Both a graphical network and a tabular summary are available on the right panel. Yellow, green, orange and pink denote SNPs, genes, disease/traits, and parent terms, respectively. Node size is proportionate to the number of connections that node has in the GWAS catalog database. The figure displays pleiotropic network results for the gene *CDKN2B-AS1*

Acknowledgements

This study makes use of data collected in the GWAS catalog.

Funding

This work was supported in part by National Institutes of Health (NIH; Bethesda, MD, USA) [grants R01EY022651, R01EY027315 and RF1AG060472]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Conflict of Interest: none declared.

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