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QTL Mapping via GeneNetwork.org

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We use this protocol and it's working

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Disclaimer

This work is done using the resources provided by GeneNetwork.org, all citation guidelines should be according to the data used.

Abstract

The use of GeneNetwork.org for identifying quantitative trait loci. Rich datasets available for mapping a wide range of traits to genomic variation.

Introduction

1 **Quantitative trait loci (QTL) mapping using GeneNetwork.org:**

QTL mapping is a method to identify genomic regions that influence variation in a phenotypic trait.
GeneNetwork.org is a data and analytic resource for interrogating linked multimodal data, with integrating functionality for QTL mapping.

This protocol is a step-by-step guide on how to use GeneNetwork.org for QTL mapping.

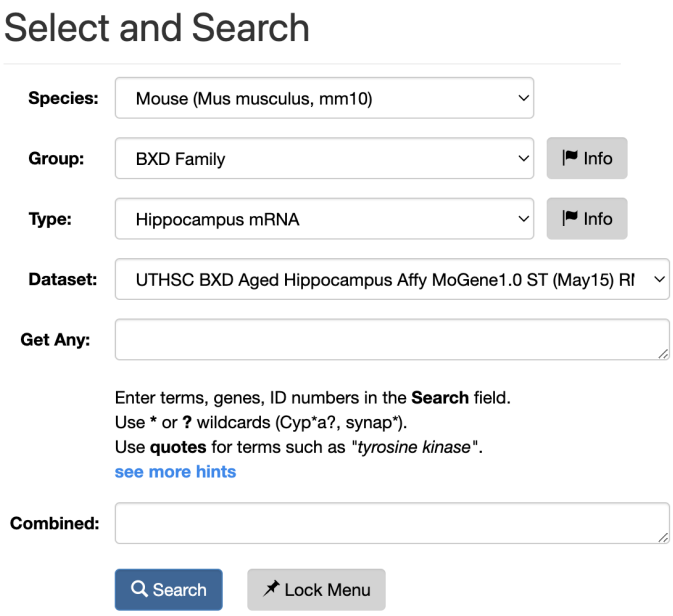
How to use GeneNetwork for QTL Mapping

2 **Accessing datasets:**

There are multiple ways to navigate to datasets of interest:

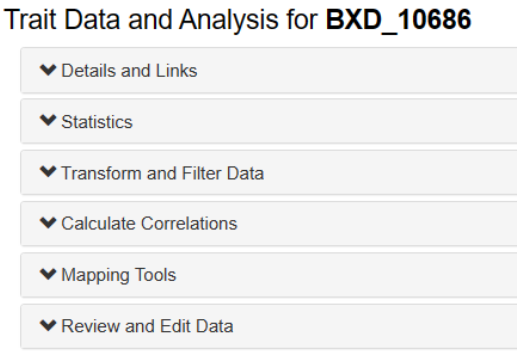
- **Option 1:** open the GeneNetwork.org homepage, select “Phenotypes” and use the search field (as highlighted in the screenshot) to search for a trait of interest. Many search options are explained in detail by clicking the "?" icon.

- **Option 2:** open the GeneNetwork.org homepage and use the multi-field search option, selecting “Species”, “Group”, “Type”, “Dataset”, etc (as indicated in the screenshot below). See "Advanced Commands" (just under Select and Search) for explanations for using the "Get Any" and "Combined" fields.



3 **Assess and prepare data for mapping:**

Once the trait webpage is open (for example https://genenetwork.org/show_trait?trait_id=10686&dataset=BXDPublish), there are multiple headers that allow the user to get an overview of various aspects of the data, as well as to calculate correlations and map QTLs. A screenshot of these headers is below, followed by a description of the corresponding utility of each section.



Details and Links:

This provides the user background information on the data, including a description, corresponding citations and linked databases

Statistics:

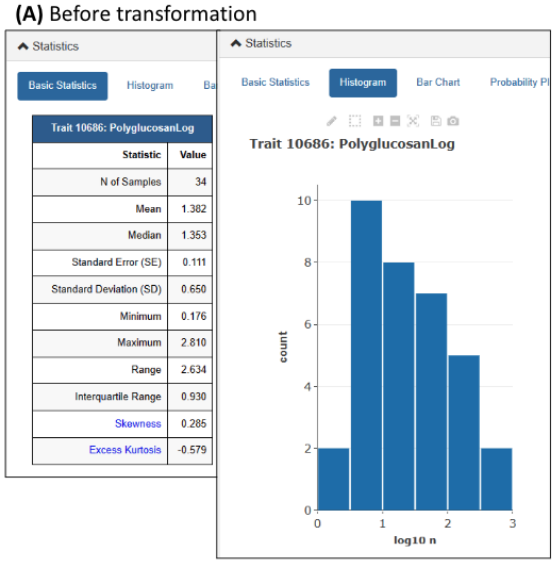
Presented here are descriptive statistics and data visualizations (including tabs for a histogram, bar chart, probability plot and violin plot of the data, which can be downloaded).
The histogram is useful to assess the data distribution. For QTL mapping using genome-wide efficient mixed-model association (GEMMA), Gaussian distributed data is a prior assumption, as QTL mapping is sensitive to outliers (Sloan ZA "Outliers" From The WebQTL Glossary--A GeneNetwork Resource. gn1.genenetwork.org/glossary.html (last accessed 9th May 2024)).

Transform and Filter Data:

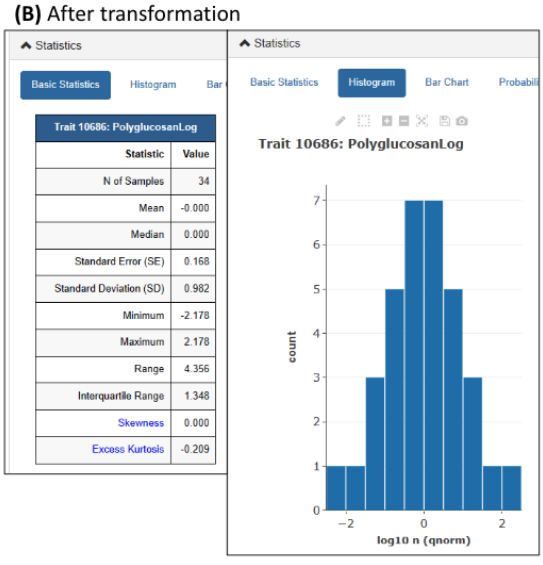
This allows the user to block samples (for example outliers which may impact mapping), filter for specific traits within the data cohort (for example transgenic or non-transgenic samples only) and normalize the data using several methods. All steps can be undone. At any point the data can be exported in .csv format.

In the case of the hippocampal polyglucosan study, the data (GeneNetwork ID: BXD_10686) was quantile normalized. The result of this data operation can be visualized by revisiting the histogram or the skewness measure in the “Statistics” section. Example screenshots below.

(A) Before transformation



(B) After transformation



Calculate Correlations:
This tab allows the user to calculate correlations with data from various databases (such as gene expression, proteomics or phenotypic trait data). The user can modify correlation parameters to allow for case specific adjustments.

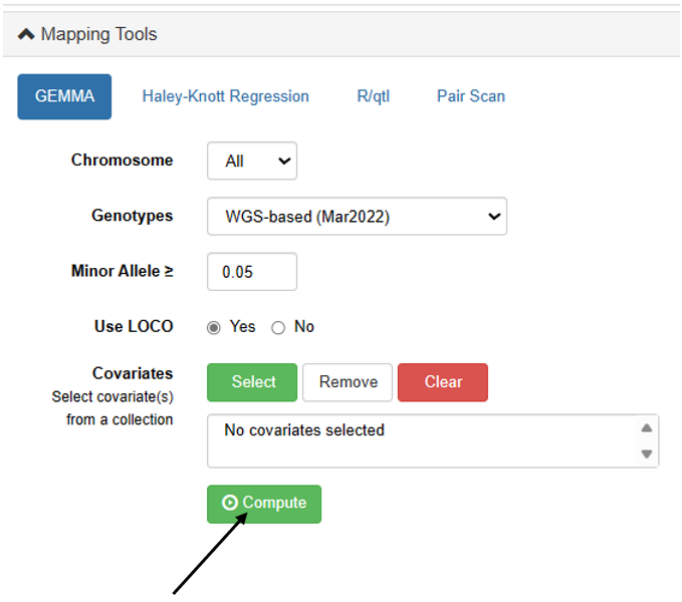
Mapping Tools:
Here, several methods for QTL mappings are available (GEMMA, Haley-Knott Regression, R/qtl version 1.44.9 and Pair Scan R/qtl version 1.44.9).

Review and Edit Data:
This tab provides the user with a samplewise overview of the samples. For example, information includes the number of animals sampled per strain (in the case of BXD mouse data).

4 QTL Mapping using GeneNetwork.org

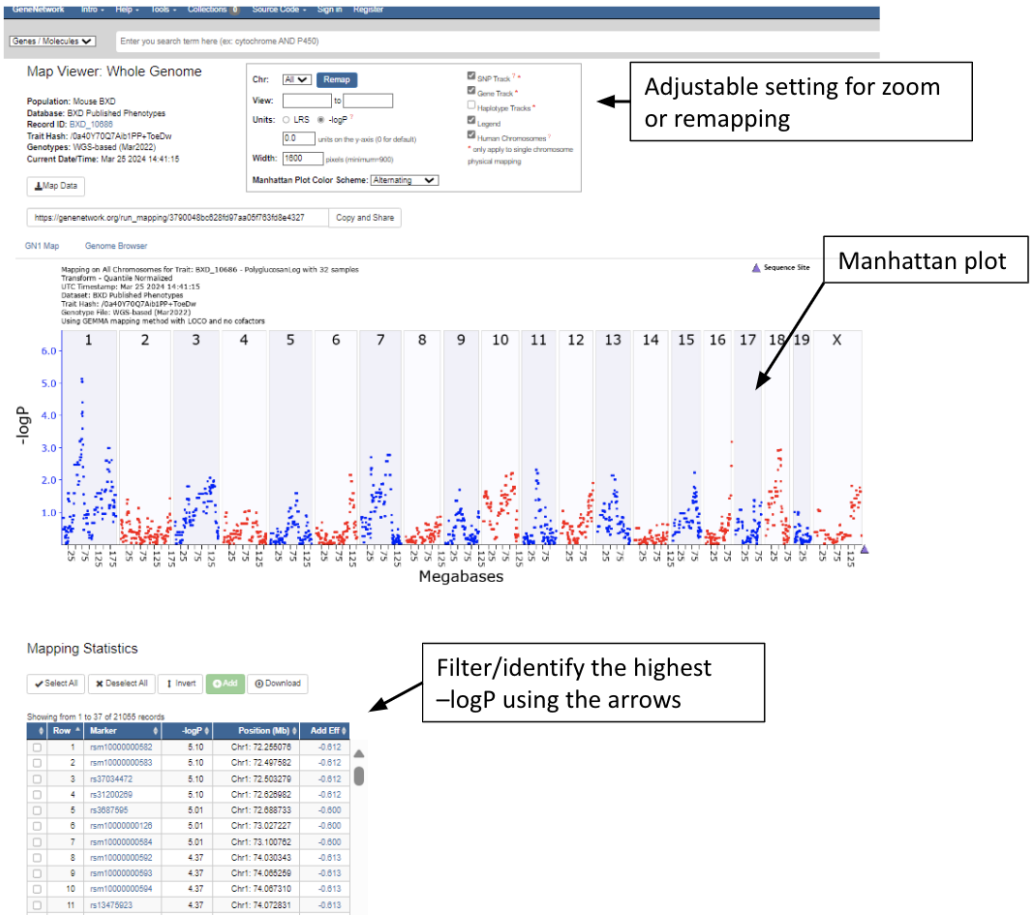
To perform QTL mapping in GeneNetwork.org, several mapping methods are available in the “Mapping Tools” tab.

In the case of the hippocampal polyglucosan study, the default parameters were used (see screenshot below). Using the green compute button, a Manhattan plot illustrating genome-wide associations of the trait of interest is displayed.



Once the computation is done, the user is presented with the Manhattan plot and can zoom into areas of the genome of interest using the indicated box at the top of the page (see screenshot below). Mapping statistics displayed below the Manhattan plot can be filtered to sort for the highest -logP of single nucleotide polymorphism (SNP) markers or by genomic location.

A QTL is narrowed down, by a 1.5 point drop in relation to the highest SNP marker. Hence a region is defined as the distance between the two most distant SNP markers showing a drop of 1.5 points from the highest scoring SNP marker (Ani Manichaikul, Josée Dupuis, Śaunak Sen, Karl W Broman, Poor Performance of Bootstrap Confidence Intervals for the Location of a Quantitative Trait Locus, *Genetics*, Volume **174**, Issue 1, 1 September 2006, Pages 481–489, https://doi.org/10.1534/genetics.106.061549).



Protocol references

Mulligan MK, Mozhui K, Prins P, Williams RW. GeneNetwork: A Toolbox for Systems Genetics. Methods Mol Biol. 2017;1488:75-120. doi: 10.1007/978-1-4939-6427-7_4. PMID: 27933521; PMCID: PMC7495243.

Ani Manichaikul, Josée Dupuis, Śaunak Sen, Karl W Broman, Poor Performance of Bootstrap Confidence Intervals for the Location of a Quantitative Trait Locus, *Genetics*, Volume 174, Issue 1, 1 September 2006, Pages 481–489, https://doi.org/10.1534/genetics.106.061549