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EnigmaVis: online interactive visualization of genome-wide association studies of the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium

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Summary

In an attempt to increase power to detect genetic associations with brain phenotypes derived from human neuroimaging data, we recently conducted a large-scale genome-wide association meta-analysis of hippocampal, brain, and intracranial volume through the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium. Here we present a freely-available online interactive tool, EnigmaVis, which makes it easy to visualize the association results generated by the consortium alongside allele frequency, genes, and functional annotations. EnigmaVis runs natively within the web browser, and generates plots that show the level of association between brain phenotypes at user-specified genomic positions. Uniquely, EnigmaVis is dynamic; users can interact with elements on the plot in real time. This software will be useful when exploring the effect on brain structure of particular genetic variants influencing neuropsychiatric illness and cognitive function. Future projects of the consortium and updates to EnigmaVis will also be displayed on the site. EnigmaVis is freely available online at <http://enigma.loni.ucla.edu/enigma-vis/>.

The human brain has many heritable features (Kremen et al., 2010; Peper et al., 2007; Thompson et al., 2001). However, the genetic variants underlying these high heritability estimates are, for the most part, unknown. Genome-wide association studies (GWAS) are one way to identify common variants influencing heritable traits in large-scale population studies. GWAS have been used to identify associations between single-nucleotide polymorphisms (SNPs) and a host of different traits implicated in numerous diseases (Cichon et al., 2009; McCarthy et al., 2008). Meta-analysis has proven to be critical to our understanding of the true effects that specific genetic variants have on these traits, as most common variants have small effects. In general, individual studies – which typically assess a few hundred to a thousand individuals – are underpowered to reliably detect associations. Recently, we initiated the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium (Stein et al., 2012). The primary goal of the ENIGMA consortium is to expedite meta-analysis of large datasets and create a forum for collaboration in the field of imaging genetics. The effort is modeled on other highly successful consortia in psychiatric genetics, which have discovered genetic loci associated with bipolar illness, schizophrenia, and ADHD (Neale et al., 2010; Ripke et al., 2011; Sklar et al., 2011), offering new leads for research at the molecular and systems levels. In several ongoing projects, the ENIGMA consortium has been analyzing the genetic influences on

neuroimaging traits with data from over 20 research groups and tens of thousands of subjects. This presents a useful resource for the imaging, neuropsychiatric, and cognitive genetics communities to discover genes that influence the brain. It also facilitates the confirmation, replication and understanding of effects of promising genetic variations and pathways.

A method for user-friendly visualization and navigation of the genetic regions containing important associations is essential for demonstrating significant findings and distributing these results. For initiatives such as ENIGMA, analyzing very large amounts of GWAS data, it is critical that researchers are able to quickly and efficiently examine the strength of the association at any desired genetic loci. Specifically, researchers may want to look up the evidence of genetic association between a gene they are interested in, and various brain measures examined by ENIGMA. As such, a visualization utility may prove to be one of the most useful methods to facilitate interpretation of ENIGMA results. Conventional publication formats for GWAS make it difficult for those not closely involved in the study to access and browse the results. Top hits are usually summarized in tables, which lose a great deal of the data that is available at other loci across the genome. Additionally, conventional formats rely on non-visual methods for data presentation, often consisting of lists of SNP numbers and probabilities of association that are very hard to digest. Existing online data visualization tools – SzGene, AlzGene, LocusZoom, Ricopili – for genetic association studies (Allen et al., 2008; Bertram et al., 2007; Pruim et al., 2010; Ripke & Thomas, 2011) are available but with some limitations. All of these existing tools are static in nature, and the SzGene/AlzGene databases are based primarily on candidate-gene studies only. Additionally, these tools are not available for imaging genetics data. To this end, we developed EnigmaVis, an online interactive tool for visualizing unbiased genome-wide association results from ENIGMA.

Implementation

Features and functionality

The main EnigmaVis webpage (<http://enigma.loni.ucla.edu/enigma-vis/>) features a query box and phenotype selection drop-down box. These fields allow a user to query the database of associations with neuroimaging phenotypes generated by the ENIGMA consortium and generate custom, interactive plots for a desired region of the genome. The user can search by SNP, genomic position, or gene. Optionally, the user can also specify flanking region sizes. After creating and submitting a query, an interactive plot is generated.

The plot displays the genomic position of the user's query, in basepairs, on the x-axis, and $-\log_{10}(p)$ representing the evidence for genetic association between that genomic locus and a trait (e.g., hippocampal volume) on the y axis, at the left. SNPs are represented on the plot as circles, with the minor allele frequency represented by the radius of the circle (see Fig 1). Recombination rate (cM/Mb), attained from the HapMap 3 project, is represented as a filled curve beneath the SNP datapoints, and corresponds to the labels on the y axis at the right hand side of the plot (Altshuler et al., 2010). Below the main plot, EnigmaVis displays the position of genes and their exons from the UCSC Genome Browser (Kent et al., 2002). For direct SNP queries, the SNP of interest is indicated on the plot by a vertical line. EnigmaVis uses the NCBI 36/hg18 build of the human genome.

Elements on the plot are interactive. By hovering over a SNP within the plot, the user can display a tooltip providing information about the SNP, including its identifier, chromosome and basepair location, effect allele frequency, meta-analytic p-value, meta-analytic effect size and meta-analytic standard error (see Fig 2). Similarly, the user can hover over a gene to reveal information about the gene. EnigmaVis supports plot navigation in two ways: 1)

the user can “zoom in” (plot a subset of the currently displayed SNPs) by dragging a desired region directly onto the plot, and 2) the user can pan the plot upstream or downstream by clicking on arrows to the left and right of the plot.

Implementation Details

EnigmaVis is comprised of a client-side front-end, a server-side back-end, and a MySQL database. The front-end, which contains the plotting engine and query fields, was written in JavaScript and HTML5 using the Raphaël JavaScript vector graphics library. Using custom software, the MySQL database was populated with data from ENIGMA, the UCSC Genome browser, and HapMap 3. The back-end was written in PHP; this code parses the user's query, retrieves all necessary data from the database, and serves it to the front-end for visualization. Most queries are typically served in less than three seconds, though queries of larger regions may require up to 20–30 seconds before a plot can be generated.

EnigmaVis can run natively in all major internet browsers without requiring the installation of any third party software or add-ons. It only requires that the browser version be recent enough to provide HTML5 support. The main webpage (<http://enigma.loni.ucla.edu/enigma-vis/>) features documentation of valid query forms that the user can use to generate plots, as well as features of the application itself. No account or login information is required to use EnigmaVis.

Future implementations

As EnigmaVis is still an active, ongoing project, additional features are currently planned for implementation in the future. We aim to find creative ways for users to visualize multiple phenotype associations on the same plot, and identify putative functional significance of SNPs in a manner that takes advantage of the interactive nature of EnigmaVis. The user could, for example, be allowed to plot the LD to annotated SNPs with functional potential (coding non-synonymous, splice site, 5' and 3' UTR). Visualization of multiple phenotype associations simultaneously would be useful for identifying loci with a pleiotropic effect, a situation in which a single gene has an influence on multiple phenotypes. In the future, we also aim to provide on-the-fly meta-analysis. For example, people often want to know if the cohort effect generalizes to the samples they are interested in. Future implementations will allow users to see how much the association probabilities change if the populations on which they are based (e.g., ethnicity) are changed on the fly.

Conclusions

We present EnigmaVis, an intuitive, online tool allowing users to visualize and navigate through ENIGMA datasets by generating interactive plots. The tool provides, for the first time, a straightforward way to visually examine the large quantities of data collected through the ENIGMA consortium. EnigmaVis is OS-independent, accessible through all common web browsers, and does not require installation of special software. Uniquely, EnigmaVis is interactive; once a plot has been generated by a user query, elements on the plot can be interacted with in a live fashion, without generating a new plot. As such, our approach enables interactive interrogating capabilities, tightly coupling the data to analysis and facilitating discovery. EnigmaVis is easily maintainable and is, at present, still an active project. In the future, support will be provided for visualizing additional phenotypes as the data become available (as well as the simultaneous visualization of multiple phenotypes on the same plot), and we anticipate that new features will be implemented which build upon the unique interactive capabilities of EnigmaVis.

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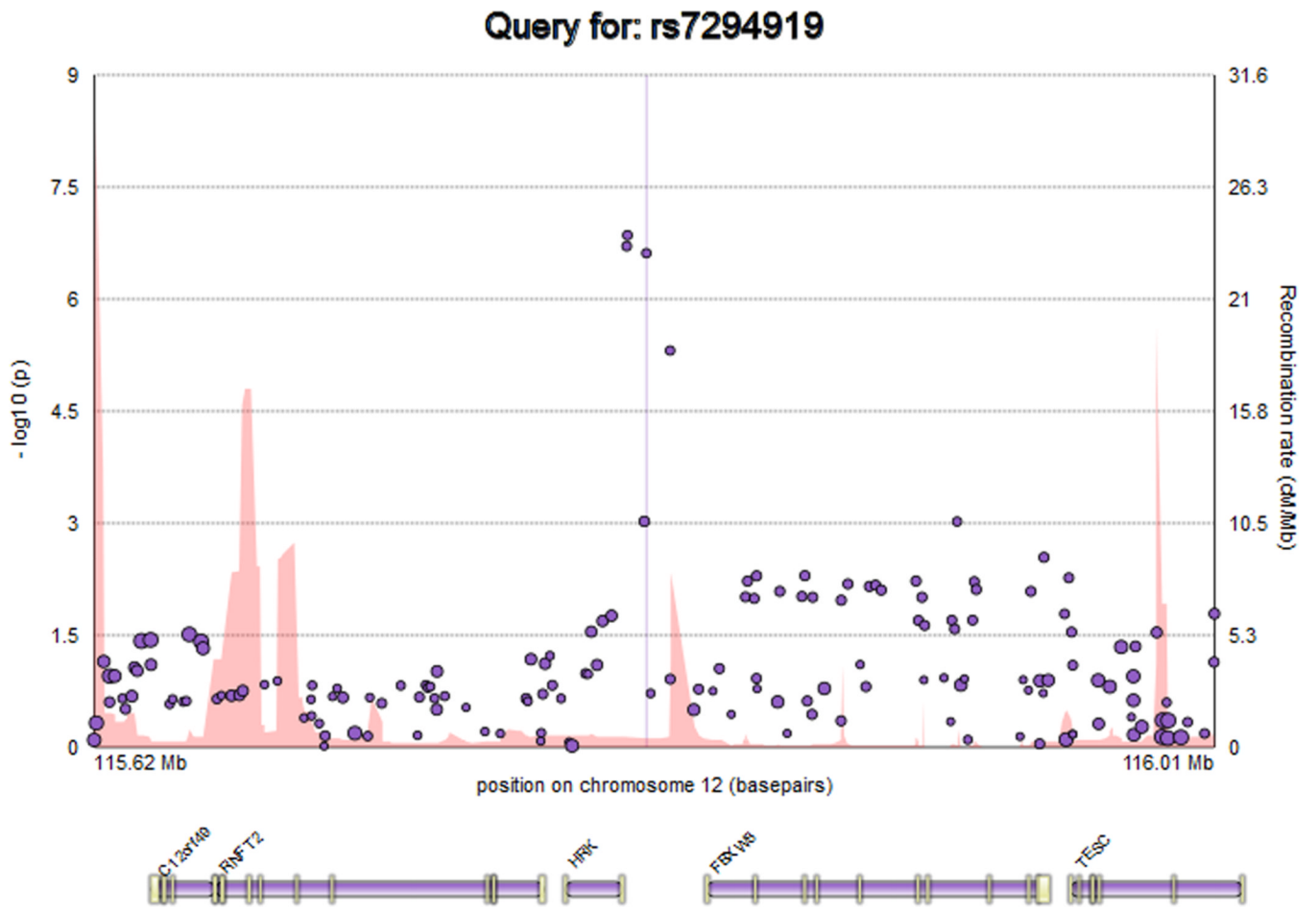


Figure 1.
The EnigmaVis plot

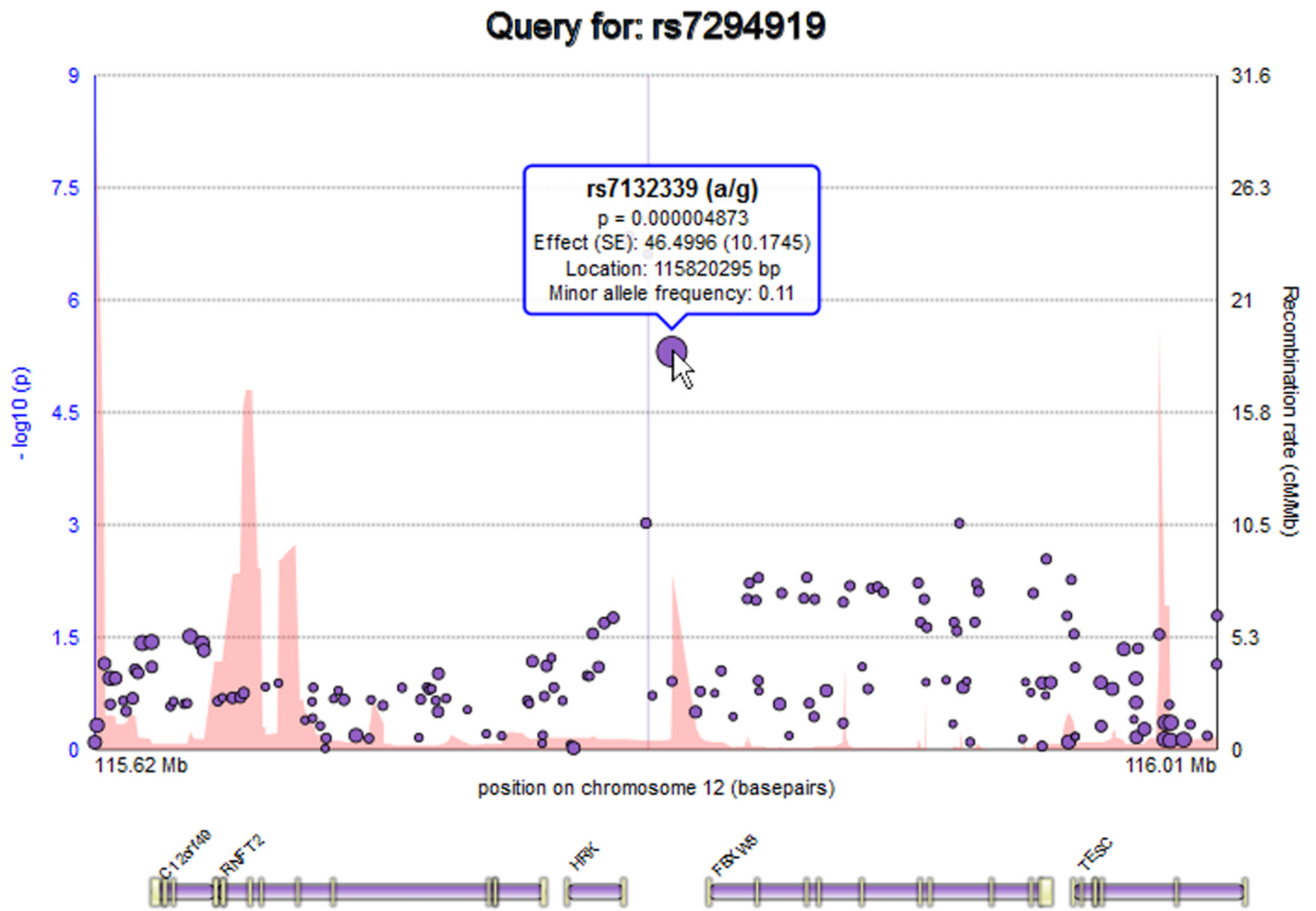


Figure 2. The EnigmaVis Plot, showing the tooltip that appears when the user hovers over a particular SNP. Not shown: "panning" navigation buttons allow the user to navigate upstream or downstream of the current view.