

## Subject Section

# Visualizing the Geography of Genetic Variants

Joseph H. Marcus<sup>1</sup> and John Novembre<sup>1, 2,\*</sup>

<sup>1</sup>Department of Human Genetics, University of Chicago, Chicago, 60637, US and

<sup>2</sup>Department of Ecology and Evolution, University of Chicago, Chicago, 60637, US.

\*To whom correspondence should be addressed.

Associate Editor: XXXXXXXX

Received on XXXXX; revised on XXXXX; accepted on XXXXX

## Abstract

One of the key characteristics of any genetic variant is its geographic distribution. The geographic distribution can shed light on where an allele first arose, what populations it has spread to, and in turn on how migration, genetic drift, and natural selection have acted. The geographic distribution of a genetic variant can also be of great utility for medical/clinical geneticists and collectively many genetic variants can reveal population structure. Here we develop an interactive visualization tool for rapidly displaying the geographic distribution of genetic variants. Through a REST API and dynamic front-end the *Geography of Genetic Variants (GGV)* browser provides maps of allele frequencies in populations distributed across the globe.

**Contact:** jhmarcus@uchicago.edu, jnovembre@uchicago.edu

**Supplementary information:** Supplementary data are available at *Bioinformatics* online.

## 1 Introduction

Genetics researchers often face the problem that they have identified one or many genetic variants of interest using an approach such as a genome-wide association study and then would like to know the geographic distribution of the variant. For example, the researcher may hope to address: 1) implications for genomic medicine (e.g. Is a risk allele geographically localized to a certain patient population? What population should be studied to observe variant carriers? Rosenberg *et al.*, 2010); or 2) the evolutionary history of the variant in question (e.g. does the variant correlate with a known environmental factor in a manner suggestive of some geographically localized selection pressure? Novembre and Di Rienzo, 2009; Coop *et al.*, 2010). A simple geographic map of the distribution of a genetic variant can be incredibly insightful for these questions.

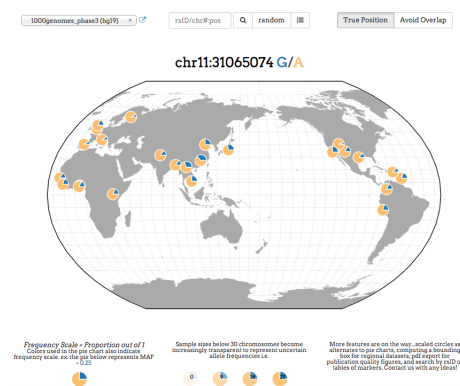
Contemporary population genetics researchers are also faced with the challenge of large, high-dimensional datasets. For example, it is not uncommon for a researcher in human genetics to have a dataset comprised of thousands of individuals measured at hundreds of thousands or even millions of single nucleotide variants (SNVs). One common approach to visualizing such high-dimensional data is to compress the SNV dimensions down to a small number of latent factors, using a method such as principal components analysis (Price *et al.*, 2006; Patterson *et al.*, 2006), or a model-based clustering method such as STRUCTURE (Pritchard *et al.*, 2000) or ADMIXTURE (Alexander *et al.*, 2009). While these methods are

extremely valuable, researchers can use them too often without inspecting the underlying variant data in more detail. A natural approach to gaining more insight to the overall structure of a population genetic dataset is to visually inspect what geographic patterns arise in allele frequency maps.

Unfortunately, generating geographic allele frequency maps is time-consuming for the average researcher as it requires a combination of data-wrangling methods (Kandel *et al.*, 2011) and map-making techniques that are unfamiliar to most. Our aim here is to produce a tailored system for rapidly constructing informative geographic maps of allele frequency variation.

Our work is inspired by past tools such as the ALFRED database (Rajeevan *et al.*, 2012) and the maps available on the HGDP Selection browser (Pickrell *et al.*, 2009) whose allele frequency output and plots have been used in research articles (e.g. Pickrell *et al.*, 2009; Coop *et al.*, 2009), books (e.g. Dudley and Karczewski, 2013), and have been made available on the UCSC Genome Browser (available under the HGDP Allele Freq track of the browser Kent *et al.*, 2002).

Taking advantage of recent advances in web-based visualization tools (Bostock *et al.*, 2011), we aim to address the significant visualization challenges that are inherent in the production of geographic allele frequency maps for large population genomic datasets (The 1000 Genomes Project Consortium, 2015), (Lazaridis *et al.*, 2014), including dynamic interaction, display of rare genetic variation, and representation of uncertainty in estimated allele frequencies due to variable sample sizes.



**Fig. 1.** Example screenshot from the Geography of Genetic Variants browser using The 1000 Genomes Project Consortium (2015) data. Each pie chart represents a population with the blue slice of the pie displaying the frequency of the global minor allele.

## 2 Approach

The Geography of Genetic Variants browser (GGV) uses the scalable vector graphics and mapping utilities of D3.js (Bostock *et al.*, 2011) to generate interactive frequency maps, allowing for quick and dynamic displays of the geographic distribution of a genetic variant. The front-end provides legends for the map and various configuration boxes to allow users to query different datasets or choose visualization options.

In order to allow for easy access to commonly used public genomic datasets, such as the 1000 Genomes project (The 1000 Genomes Project Consortium, 2015) or Human Genome Diversity project (Li *et al.*, 2008), we have developed a REST API (Grinberg, 2014) for accessing data. The API allows querying of allele frequencies by chromosome and position, by reference SNP identifier (Sherry *et al.*, 2001), or randomly sampled SNPs. After a query, the GGV displays the allele frequencies for a set of populations as a collection of pie charts where each represents the minor and major allele frequency in a single population. Pie charts are displayed as points at a latitude and longitude associated with a population and the map boundaries are chosen based off of the geographic configuration of populations in a given dataset [Figure 1].

We implement a variety of features to display the geographic distribution of genetic variants. **(1) Rare variants:** Representing the frequency of rare variants across populations can be difficult as allele frequencies between variants often differ greatly (e.g. The 1000 Genomes Project Consortium, 2015; Nelson *et al.*, 2012; Tennesen *et al.*, 2012). To address this challenge we re-scale frequencies for rare variants, so that small frequencies become visible. Specifically, we use a frequency scale that is indicated in a legend below the map and represented by varying color in the pie charts [Figure 1, Supplementary Figure S1, Supplementary Table S1]. **(2) Uncertainty in frequency data:** We use varying transparency in a population's pie chart: estimated frequencies with higher levels of sampling error (e.g. those from samples with  $n < 30$ ) are made more transparent, and hence less visible, on the map [Figure 1, Supplementary Figure S2]. **(3) Overlapping populations:** We use force-directed layouts of the populations such that no two points are overlapping each other, and yet the points will be pulled towards their true origins [Figure 1, Supplementary Figure S3]. Also, by hovering the mouse cursor over any population, a user can see the population labels and precise frequency information.

By allowing rapid generation of allele frequency maps, we hope to facilitate the interpretation of variant function and history by practicing geneticists. Also, for students of human diversity, it is often difficult to conceptualize classic statements regarding how most variation in humans

is shared among populations (Lewontin, 1972) and how the fixation index  $F_{ST}$  is relatively low globally (10-15% The 1000 Genomes Project Consortium, 2015). We hope that the ability to query random variants from major human population genetic samples will allow students to appreciate the structure of human genetic diversity in an approachable and intuitive form.

## Acknowledgements

We acknowledge the Research Computer Center at the University of Chicago, especially H. Birali Runesha, Jeff Tharsen, Richard Williams, and Alex Mueller, for on-going support and extensions of the GGV browser. We also thank John Zekos for web server administration and support. The authors would also like to thank members of the Novembre Lab for supportive conversations. Support for this work was provided by the National Institutes of Health via the Big Data to Knowledge initiative (1U01 CA198933-0) to JN and the National Institute Of General Medical Sciences under training grant award number T32GM007197 for JHM. The content is solely the responsibility of the authors and does not necessarily reflect the official view of the National Institutes of Health.

## References

- Alexander, D. H., Novembre, J., and Lange, K. (2009). Fast model-based estimation of ancestry in unrelated individuals. *Genome Research*, **19**(9), 1655–1664.
- Bostock, M., Ogievetsky, V., and Heer, J. (2011). D<sup>3</sup> data-driven documents. *IEEE Transactions on Visualization and Computer Graphics*, **17**(12), 2301–2309.
- Coop, G., Pickrell, J. K., Novembre, J., Kudaravalli, S., Li, J., Absher, D., Myers, R. M., Cavalli-Sforza, L. L., Feldman, M. W., and Pritchard, J. K. (2009). The role of geography in human adaptation. *PLoS Genet*, **5**(6), e1000500.
- Coop, G., Witonsky, D., Di Rienzo, A., and Pritchard, J. K. (2010). Using environmental correlations to identify loci underlying local adaptation. *Genetics*, **185**(4), 1411–1423.
- Dudley, J. T. and Karczewski, K. J. (2013). *Exploring personal genomics*. Oxford University Press.
- Grinberg, M. (2014). *Flask Web Development: Developing Web Applications with Python*. O'Reilly Media, Inc.
- Kandel, S., Heer, J., Plaisant, C., Kennedy, J., van Ham, F., Riche, N. H., Weaver, C., Lee, B., Brodbeck, D., and Buono, P. (2011). Research directions in data wrangling: Visualizations and transformations for usable and credible data. *Information Visualization*, **10**(4), 271–288.
- Kent, W. J., Sugnet, C. W., Furey, T. S., Roskin, K. M., Pringle, T. H., Zahler, A. M., and Haussler, D. (2002). The human genome browser at UCSC. *Genome Research*, **12**(6), 996–1006.
- Lazaridis, I., Patterson, N., Mittnik, A., Renaud, G., Mallick, S., Kirsanow, K., Sudmant, P. H., Schraiber, J. G., Castellano, S., Lipson, M., *et al.* (2014). Ancient human genomes suggest three ancestral populations for present-day Europeans. *Nature*, **513**(7518), 409–413.
- Lewontin, R. C. (1972). The apportionment of human diversity. *Evolutionary Biology*, **6**, 381–398.
- Li, J. Z., Absher, D. M., Tang, H., Southwick, A. M., Casto, A. M., Ramachandran, S., Cann, H. M., Barsh, G. S., Feldman, M., Cavalli-Sforza, L. L., *et al.* (2008). Worldwide human relationships inferred from genome-wide patterns of variation. *Science*, **319**(5866), 1100–1104.
- Nelson, M. R., Wegmann, D., Ehm, M. G., Kessner, D., Jean, P. S., Verzilli, C., Shen, J., Tang, Z., Bacanu, S.-A., Fraser, D., *et al.* (2012). An abundance of rare functional variants in 202 drug target genes sequenced in 14,002 people. *Science*, **337**(6090), 100–104.
- Novembre, J. and Di Rienzo, A. (2009). Spatial patterns of variation due to natural selection in humans. *Nature Reviews Genetics*, **10**(11), 745–755.
- Patterson, N., Price, A. L., and Reich, D. (2006). Population structure and eigenanalysis. *PLoS Genet*, **2**(12), e190.
- Pickrell, J. K., Coop, G., Novembre, J., Kudaravalli, S., Li, J. Z., Absher, D., Srinivasan, B. S., Barsh, G. S., Myers, R. M., Feldman, M. W., *et al.* (2009). Signals of recent positive selection in a worldwide sample of human populations. *Genome Research*, **19**(5), 826–837.
- Price, A. L., Patterson, N. J., Plenge, R. M., Weinblatt, M. E., Shadick, N. A., and Reich, D. (2006). Principal components analysis corrects for stratification in genome-wide association studies. *Nature Genetics*, **38**(8), 904–909.

- Pritchard, J. K., Stephens, M., and Donnelly, P. (2000). Inference of population structure using multilocus genotype data. *Genetics*, **155**(2), 945–959.
- Rajeevan, H., Soundararajan, U., Kidd, J. R., Pakstis, A. J., and Kidd, K. K. (2012). ALFRED: an allele frequency resource for research and teaching. *Nucleic Acids Research*, **40**(D1), D1010–D1015.
- Rosenberg, N. A., Huang, L., Jewett, E. M., Szpiech, Z. A., Jankovic, I., and Boehnke, M. (2010). Genome-wide association studies in diverse populations. *Nature Reviews Genetics*, **11**(5), 356–366.
- Sherry, S. T., Ward, M.-H., Kholodov, M., Baker, J., Phan, L., Smigielski, E. M., and Sirotkin, K. (2001). dbSNP: the NCBI database of genetic variation. *Nucleic Acids Research*, **29**(1), 308–311.
- Tennessen, J. A., Bigham, A. W., O'Connor, T. D., Fu, W., Kenny, E. E., Gravel, S., McGee, S., Do, R., Liu, X., Jun, G., *et al.* (2012). Evolution and functional impact of rare coding variation from deep sequencing of human exomes. *Science*, **337**(6090), 64–69.
- The 1000 Genomes Project Consortium (2015). A global reference for human genetic variation. *Nature*, **526**(7571), 68–74.