

Visualizing the Geography of Genetic Variants

Joseph H. Marcus^{*1} and John Novembre^{*1,2}

¹Department of Human Genetics, University of Chicago, Chicago, IL, USA

²Department of Ecology and Evolutionary Biology, University of Chicago, Chicago, IL, USA

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 distribution of a genetic variant can also be of great utility for medical/clinical geneticists. Collectively the geographic distribution of many genetic variants can reveal population structure. As a result, visual inspection of geographic maps for genetic variants is common practice in genetic studies. 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.

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 approaches 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). One of us (JN) developed the scripts

* Address correspondence to JHM (jhmarius@uchicago.edu) or JN (jnovembre@uchicago.edu).

40 for the HGDP Selection Browser maps using The Generic Mapping Tools (GMT) (WESSEL *et al.*, 2013), a
41 powerful system of geographic plotting scripts for making static plots. The plots from the HGDP Selection
42 Browser have proved useful, have appeared in research articles (e.g. PICKRELL *et al.*, 2009; COOP *et al.*,
43 2009), books (e.g. DUDLEY and KARCZEWSKI, 2013), and have been made available on the UCSC Genome
44 Browser (available under the HGDP Allele Freq track of the browser KENT *et al.*, 2002).

45 Reference datasets for population genetic variation have greatly expanded since the release of the HGDP
46 Illumina 650Y dataset (LI *et al.*, 2008) that formed the basis of the HGDP Selection Browser maps. The
47 most notable advance is the publication of the 1000 Genomes Phase 3 data (THE 1000 GENOMES PROJECT
48 CONSORTIUM, 2015) though additional datasets are continually coming online (e.g. LAZARIDIS *et al.*, 2014).
49 In addition, novel approaches for data visualization have become more widely available. In particular, web-
50 based visualization tools, such as Data Driven Documents (D3.js), offer useful methods for interactivity, the
51 advantages of software development in modern web-browsers, a large open-source development community,
52 and ease of sharing (BOSTOCK *et al.*, 2011).

53 Taking advantage of these recent advances, we aim to address the significant visualization challenges that
54 are inherit in the production of geographic allele frequency maps, including dynamic interaction, display
55 of rare genetic variation, and representation of uncertainty in estimated allele frequencies due to variable
56 sample sizes.

57 Fundamental Approach

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

62 In order to allow for easy access to commonly used public genomic datasets, such as the 1000 Genomes
63 project (THE 1000 GENOMES PROJECT CONSORTIUM, 2015) or Human Genome Diversity project (LI *et al.*,
64 2008), we have developed a REST API (GRINBERG, 2014) for accessing data. The API allows querying of
65 allele frequencies by chromosome and position, by reference SNP identifier (SHERRY *et al.*, 2001), or randomly
66 sampled SNPs. While many applications require inspection of the distribution of a specific variant, from our
67 experience, it can be very helpful to view the geographic distribution of several randomly chosen variants to
68 quickly gain a sense of structure in a dataset. We find this to be especially useful in teaching contexts, as it
69 provides a highly visual way for learners to understand human genetic variation.

70 After a query, the GGV displays the allele frequencies for a set of populations as a collection of pie charts
71 where each represents the minor and major allele frequency in a single population. Pie charts are displayed
72 as points at a latitude and longitude assoicated with a population and the map boundaries are chosen based
73 off of the geographic configuration of populations in a given dataset [Figure 1].

74 Representing uncertainty in frequency data

75 One under-appreciated problem with allele frequency maps is that not all data points have equal levels of
76 certainty. For some locations, sample sizes are small, and the reported allele frequency may be quite far from
77 the true population frequency due to sampling error. To address this issue, we use varying transparency in
78 a population's pie chart: estimated frequencies with higher levels of sampling error (e.g. those from samples
79 with $n < 30$) are made more transparent, and hence less visible, on the map [Figure 2].

80 Representing rare variants in frequency data

81 An additional challenge is that allele frequencies between variants often differ greatly, sometimes by orders
82 of magnitude in a single dataset. This has not been a pervasive problem until recently, as most population
83 genetic samples were genotyped on SNP arrays, which have been biased towards variants that are common in



Frequency Scale = Proportion out of 1
Colors used in the pie chart also indicate frequency scale. ex. the pie below represents MAF 0.25

Sample sizes below 30 chromosomes become increasingly transparent to represent uncertain allele frequencies i.e.

More features are on the way...scaled circles as alternates to pie charts, computing a bounding box for regional datasets, pdf export for publication quality figures, and search by rsID or tables of markers. Contact us with any ideas!



Figure 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 and the yellow slice of the pie displaying the frequency of the global major allele in each population.

84 human populations (5-50 % in minor allele frequency). With the combination of next generation sequencing
 85 technologies, new array designs focusing on rarer variants, and studies with thousands of individuals or more,
 86 it is now routine for the majority of variants to be rare (e.g. THE 1000 GENOMES PROJECT CONSORTIUM,
 87 2015; NELSON *et al.*, 2012; TENNESSEN *et al.*, 2012). In visualization schemes using proportional area to
 88 represent frequency (such as standard pie charts), rare variants would be represented as narrow slivers,
 89 nearly invisible to the naked eye.

90 To address this challenge we re-scale frequencies for rare variants, so that small frequencies become visible.
 91 Specifically, we use a frequency scale that is indicated in a legend below the map and represented by varying
 92 color in the pie charts [Figure 3]. Much like scientific notation, this allows a wide range of frequencies to be
 93 displayed (Table 1).

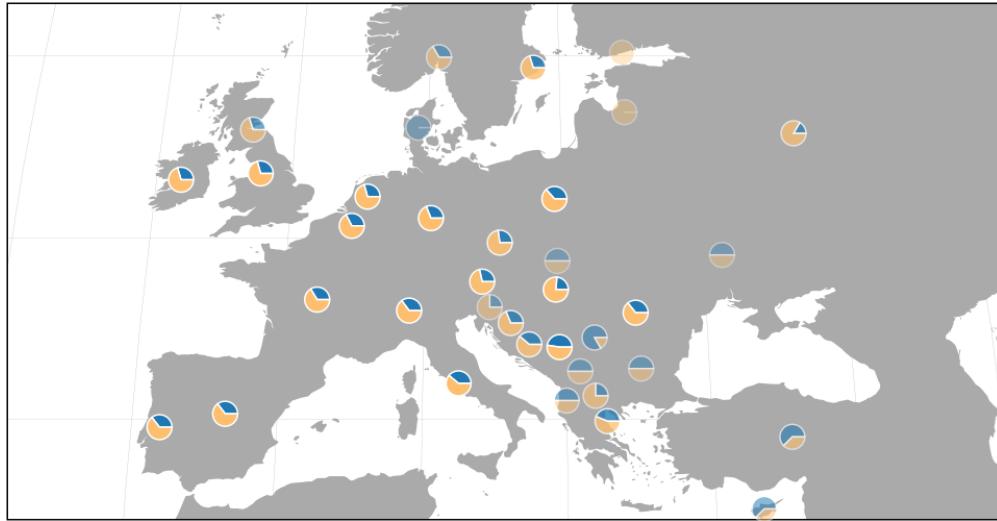


Figure 2: Example map from the Geography of Genetic Variants browser displaying the use of varying transparency of population pie charts to represent uncertainty in allele frequencies. The transparency is scaled in proportion to the number of observed chromosomes in each population for a particular variant. The frequency data and population identifiers are from NOVEMBRE *et al.* (2008).

Sample Frequency	Display Frequency Scale	Displayed Image
0.25	1	
0.025	0.1	
0.0025	0.01	
0.00025	0.001	

Table 1: Rare variants present a challenge for display. To address this challenge, the GGV browser changes the displayed image and the frequency scale of the map depending on the input sample frequency. As an example, a variant with a frequency 0.0025 is shown as a pie-chart that is 25% full and a frequency scale of 0.01 is marked in the legend of the map.

94 Additional features of the interface

95 In many datasets where populations are sampled densely in geographic space, one problem is that allele
 96 frequency plots begin to overlap each other and obscure information. To address this issue, we use force-
 97 directed layouts of the populations such that no two points are overlapping each other, and yet the points
 98 will be pulled towards their true origins [Figure 5]. Also, by hovering the mouse cursor over any population,
 99 a user can see the population labels and precise frequency information.

100 Access to the underlying frequency data

101 To provide an interface to the population minor allele frequency data, we use a REST API implemented
 102 in the python library Flask-RESTful (GRINBERG, 2014). The front-end D3.js visualization uses the API to
 103 obtain the data, though users can also interface with it directly. For the front-end, HTTP GET requests

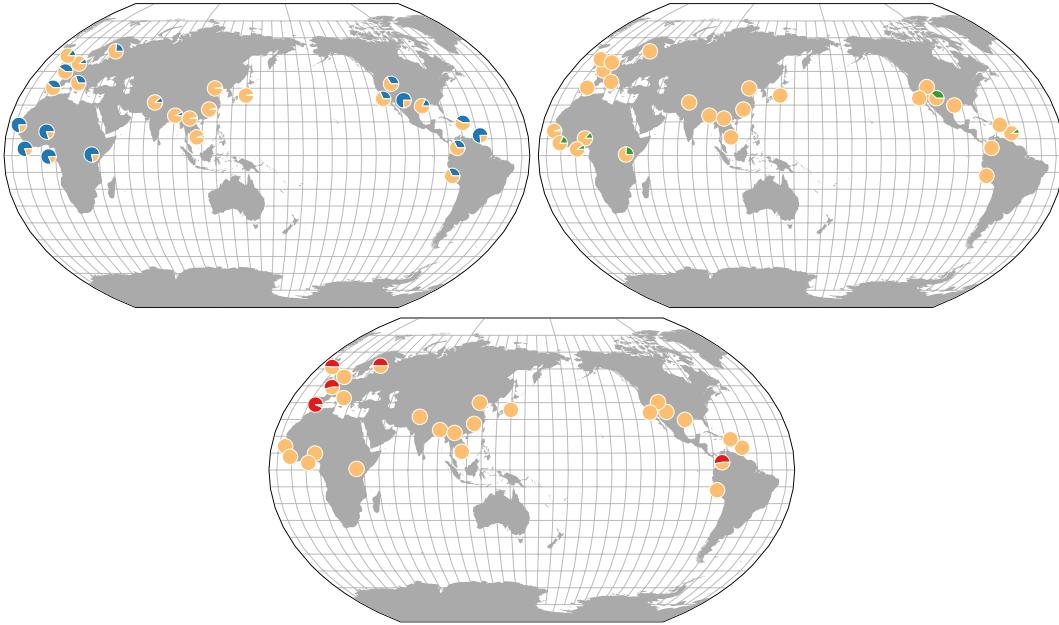


Figure 3: Example maps from the Geography of Genetic Variants browser displaying the use of frequency scales for more expressive representations of rare variation on geographic maps. The blue pie charts convey a given minor allele frequency out of 100 percent, the green out of 1 percent, and the red out of 0.01 percent. The data are from THE 1000 GENOMES PROJECT CONSORTIUM (2015).

104 return json formatted allele frequency data and the meta-data associated with each population and genetic
 105 variant (e.g. latitude, longitude, population label, sample size, and frequency scale). Genetic variants can be
 106 queried by chromosome position, rsid, or randomly. Example HTTP requests and json response can be seen
 107 in the Appendix.

108 Discussion

109 By allowing rapid generation of allele frequency maps, we hope to facilitate the interpretation of variant
 110 function and history by practicing geneticists. We also hope the ability to query random variants from major
 111 human population genetic samples will allow students to appreciate the structure of human genetic diversity
 112 in a more approachable and intuitive form than alternative visualizations.

113 A major challenge of using a geographic representation of genetic variation in humans is that the samples
 114 must be associated with a geographic location. While doing so is generally immensely helpful, it has inherent
 115 complexity and limitations. For example, practitioners must make choices regarding representing where an
 116 individual was sampled for the study (e.g. the city of a major research center) or choosing a location that
 117 is more representative of an individual's ancestral origins (e.g. based on the birthplaces of recent ancestors,
 118 such as grandparents). We do not proscribe a general solution to this problem, and for the current defaults we
 119 use locations based on the approach taken in the source publications. A future feature will allow alternative
 120 location schemas to be used for the populations in a dataset.

121 We also envision a variety of future extensions to the GGV that would allow for further dissection of
 122 geographic structure in large-scale population genomic datasets. Providing an interactive means of browsing
 123 neighboring variant sites near a SNP of interest would offer a unique view into patterns of linkage dise-
 124 quilibrium around that focal SNP. This feature would be relevant to both medical geneticists conducting
 125 genome-wide association studies with interests in fine mapping as well as population geneticists interested in
 126 scanning the genome to detect signatures of positive selection. We imagine that incorporating a chromosomal

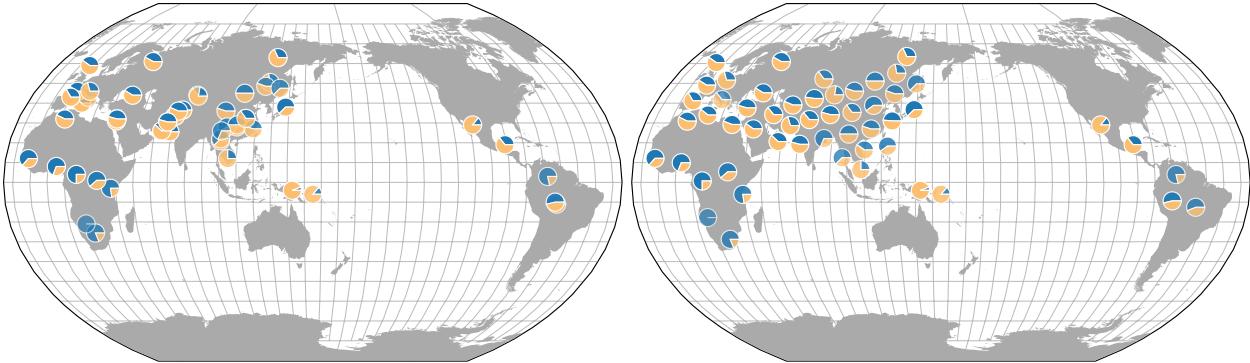


Figure 4: Example maps from the Geography of Genetic Variants browser displaying the use of a force directed layout to limit visual clutter when many populations overlap in geographic position. The left map shows the original population locations while the right shows the application of the force directed layout.

127 browser such as jbrowse (SKINNER *et al.*, 2009) within the GGV would be greatly utilized by researchers
128 and educators alike.

129 Acknowledgements

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

138 References

- 139 ALEXANDER, D. H., J. NOVEMBRE, and K. LANGE, 2009 Fast model-based estimation of ancestry in
140 unrelated individuals. *Genome Research* **19**: 1655–1664.
- 141 BOSTOCK, M., V. OGIEVETSKY, and J. HEER, 2011 D³ data-driven documents. *IEEE Transactions on*
142 *Visualization and Computer Graphics* **17**: 2301–2309.
- 143 COOP, G., J. K. PICKRELL, J. NOVEMBRE, S. KUDARAVALLI, J. LI, *et al.*, 2009 The role of geography in
144 human adaptation. *PLoS Genet* **5**: e1000500.
- 145 COOP, G., D. WITONSKY, A. DI RIENZO, and J. K. PRITCHARD, 2010 Using environmental correlations
146 to identify loci underlying local adaptation. *Genetics* **185**: 1411–1423.
- 147 DUDLEY, J. T., and K. J. KARCZEWSKI, 2013 *Exploring personal genomics*. Oxford University Press.
- 148 GRINBERG, M., 2014 *Flask Web Development: Developing Web Applications with Python*. O'Reilly Media,
149 Inc.
- 150 KANDEL, S., J. HEER, C. PLAISANT, J. KENNEDY, F. VAN HAM, *et al.*, 2011 Research directions in data
151 wrangling: Visualizations and transformations for usable and credible data. *Information Visualization* **10**:
152 271–288.

- 153 KENT, W. J., C. W. SUGNET, T. S. FUREY, K. M. ROSKIN, T. H. PRINGLE, *et al.*, 2002 The human
154 genome browser at UCSC. *Genome Research* **12**: 996–1006.
- 155 LAZARIDIS, I., N. PATTERSON, A. MITTNIK, G. RENAUD, S. MALLICK, *et al.*, 2014 Ancient human genomes
156 suggest three ancestral populations for present-day Europeans. *Nature* **513**: 409–413.
- 157 LI, J. Z., D. M. ABSHER, H. TANG, A. M. SOUTHWICK, A. M. CASTO, *et al.*, 2008 Worldwide human
158 relationships inferred from genome-wide patterns of variation. *Science* **319**: 1100–1104.
- 159 NELSON, M. R., D. WEGMANN, M. G. EHM, D. KESSLER, P. S. JEAN, *et al.*, 2012 An abundance of rare
160 functional variants in 202 drug target genes sequenced in 14,002 people. *Science* **337**: 100–104.
- 161 NOVEMBRE, J., and A. DI RIENZO, 2009 Spatial patterns of variation due to natural selection in humans.
162 *Nature Reviews Genetics* **10**: 745–755.
- 163 NOVEMBRE, J., T. JOHNSON, K. BRYC, Z. KUTALIK, A. R. BOYKO, *et al.*, 2008 Genes mirror geography
164 within Europe. *Nature* **456**: 98–101.
- 165 PATTERSON, N., A. L. PRICE, and D. REICH, 2006 Population structure and eigenanalysis. *PLoS Genet* **2**:
166 e190.
- 167 PICKRELL, J. K., G. COOP, J. NOVEMBRE, S. KUDARAVALLI, J. Z. LI, *et al.*, 2009 Signals of recent positive
168 selection in a worldwide sample of human populations. *Genome Research* **19**: 826–837.
- 169 PRICE, A. L., N. J. PATTERSON, R. M. PLENGE, M. E. WEINBLATT, N. A. SHADICK, *et al.*, 2006 Principal
170 components analysis corrects for stratification in genome-wide association studies. *Nature Genetics* **38**:
171 904–909.
- 172 PRITCHARD, J. K., M. STEPHENS, and P. DONNELLY, 2000 Inference of population structure using multi-
173 locus genotype data. *Genetics* **155**: 945–959.
- 174 RAJEEVAN, H., U. SOUNDARARAJAN, J. R. KIDD, A. J. PAKSTIS, and K. K. KIDD, 2012 ALFRED: an
175 allele frequency resource for research and teaching. *Nucleic Acids Research* **40**: D1010–D1015.
- 176 ROSENBERG, N. A., L. HUANG, E. M. JEWETT, Z. A. SZPIECH, I. JANKOVIC, *et al.*, 2010 Genome-wide
177 association studies in diverse populations. *Nature Reviews Genetics* **11**: 356–366.
- 178 SHERRY, S. T., M.-H. WARD, M. KHOLODOV, J. BAKER, L. PHAN, *et al.*, 2001 dbSNP: the NCBI database
179 of genetic variation. *Nucleic Acids Research* **29**: 308–311.
- 180 SKINNER, M. E., A. V. UZILOV, L. D. STEIN, C. J. MUNGALL, and I. H. HOLMES, 2009 JBrowse: a
181 next-generation genome browser. *Genome Research* **19**: 1630–1638.
- 182 TENNESSEN, J. A., A. W. BIGHAM, T. D. O'CONNOR, W. FU, E. E. KENNY, *et al.*, 2012 Evolution and
183 functional impact of rare coding variation from deep sequencing of human exomes. *Science* **337**: 64–69.
- 184 THE 1000 GENOMES PROJECT CONSORTIUM, 2015 A global reference for human genetic variation. *Nature*
185 **526**: 68–74.
- 186 WESSEL, P., W. H. SMITH, R. SCHARROO, J. LUIS, and F. WOBBE, 2013 Generic Mapping Tools: Improved
187 version released. *EOS, Transactions American Geophysical Union* **94**: 409–410.

188 Appendix

189 Example 1: Query by rsid

```
190 http://popgen.uchicago.edu/ggv_api/freq_table?data="1000genomes_phase3_table"&rsID=rs1834640
191 [
192   {
193     "alleles": ["A", "G"],
194     "pos": [-15.310139, "13.443182"],
195     "pop": "GWD",
196     "nobs": "226",
197     "xobs": "17",
198     "freqscale": 1,
199     "freq": [0.0752212389381, 0.9247787610619],
200     "chrom_pos": "15:48392165",
201     "rawfreq": 0.0752212389381
202   }, ...
203 ]
```

204 Example 2: Query by chromosome position

```
205 http://popgen.uchicago.edu/ggv_api/freq_table?data="1000genomes_phase3_table"&chr=14&pos=37690093
206 [
207   {
208     "alleles": ["G", "A"],
209     "pos": [-15.310139, "13.443182"],
210     "pop": "GWD",
211     "nobs": "226",
212     "xobs": "0",
213     "freqscale": 0.01,
214     "freq": [0.0, 1.0],
215     "chrom_pos": "14:37690093",
216     "rawfreq": 0.0
217   }, ...
218 ]
```

219 Example 3: Random query

```
220 http://popgen.uchicago.edu/ggv_api/freq_table?data="1000genomes_phase3_table"&random_snp=True
221 [
222   {
223     "alleles": ["T", "C"],
224     "pos": [-15.310139, "13.443182"],
225     "pop": "GWD",
226     "nobs": "226",
227     "xobs": "0",
228     "freqscale": 0.01,
229     "freq": [0.0, 1.0],
230     "chrom_pos": "5:42452893",
231     "rawfreq": 0.0
232   }, ...
233 ]
```