

Abstract

Motivation: Genome-wide datasets produced for association studies have dramatically increased in size over the past few years, with modern datasets commonly including millions of variants measured in dozens of thousands of individuals. This increase in data size is a major challenge severely slowing down genomic analyses. Specialized software for every part of the analysis pipeline have been developed to handle large genomic data. However, combining all these software into a single data analysis pipeline might be technically difficult.

Results: Here we present two R packages, `bigstatsr` and `bigsnpr`, allowing for management and analysis of large scale genomic data to be performed within a single comprehensive framework. To address large data size, the packages use memory-mapping for accessing data matrices stored on disk instead of in RAM. To perform data pre-processing and data analysis, the packages integrate most of the tools that are commonly used, either through transparent system calls to existing software, or through updated or improved implementation of existing methods. In particular, the packages implement a fast derivation of Principal Component Analysis, functions to remove SNPs in Linkage Disequilibrium, and algorithms to learn Polygenic Risk Scores on millions of SNPs. We illustrate applications of the two R packages by analysing a case-control genomic dataset for the celiac disease, performing an association study and computing Polygenic Risk Scores. Finally, we demonstrate the scalability of the R packages by analyzing a simulated genome-wide dataset including 500,000 individuals and 1 million markers on a single desktop computer.

Availability: <https://privefl.github.io/bigstatsr/> & <https://privefl.github.io/bigsnpr/>

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

1 Introduction

Genome-wide datasets produced for association studies have dramatically increased in size over the past years. A range of software and data formats have been developed to perform essential pre-processing steps and data analysis, often optimizing each of these steps within a dedicated implementation. This diverse and extremely rich software environment has been of tremendous benefit for the genetic community. However, it has two limitations: analysis pipelines are becoming very complex and researchers have limited access to diverse analysis tools due to growing data sizes.

Consider first the basic tools necessary to perform a standard genome-wide analysis. Conversions between standard file formats has become a field by itself with several tools such as VCFtools, BCFtools and PLINK, available either independently or incorporated within large framework (Danecek *et al.* 2011; Li *et al.* 2011; Purcell *et al.* 2007). Similarly, quality control software for genome-wide analysis have been developed such as PLINK and the Bioconductor package GWASTools (Gogarten *et al.* 2012). There are also several software for the computation of principal components (PCs) of genotypes, commonly performed to account for population stratification in association studies, including EIGENSOFT (SmartPCA and FastPCA) and FlashPCA (Abraham and Inouye 2014; Abraham *et al.* 2016; Galinsky *et al.* 2016; Price *et al.* 2006). Then, implementation of GWAS analyses also depends on the data format and model analyzed. For example, the software ProbABEL (Aulchenko *et al.* 2010) or SNPTEST (Marchini and Howie 2010) can handle dosage data, while PLINK version 1 is limited to best guess genotypes because of its input file format. Finally, there exists a range of tools for Polygenic Risk Scores (PRSs) such as LDpred (Vilhjalmsson *et al.* 2015) and PRSice (Euesden *et al.* 2015), which provide prediction for quantitative traits or disease risks based on multiple genetic variants. As a result, one has to make extensive bash/perl/R/python scripts to link these software together and convert between multiple file formats, involving many file manipulations and conversions. Overall, this might be a brake on data exploration.

Secondly, increasing size of genetic datasets is the source of major computational challenges and many analytical tools would be restricted by the amount of memory (RAM) avail-

63 able on computers. This is particularly a burden for commonly used analysis languages such
64 as R, Python and Perl. Solving the memory issues for these languages would give access to a
65 broad range of tools for data analysis that have been already implemented. Hopefully, strate-
66 gies have been developed to avoid loading large datasets in RAM. For storing and accessing
67 matrices, memory-mapping is very attractive because it is seamless and usually much faster
68 to use than direct read or write operations. Storing large matrices on disk and accessing them
69 via memory-mapping has been available for several years in R through “big.matrix” objects
70 implemented in the R package bigmemory (Kane *et al.* 2013). We provide a similar format as
71 filebacked “big.matrix” objects that we called “Filebacked Big Matrices (FBMs)”. Thanks to
72 this matrix-like format, algorithms in R/C++ can be developed or adapted for large genotype
73 data.

74 2 Approach

75 We developed two R packages, bigstatsr and bigsnpr, that integrate the most efficient algorithms
76 for the pre-processing and analysis of large-scale genomic data while using memory-mapping.
77 Package bigstatsr implements many statistical tools for several types of FBMs (unsigned char,
78 unsigned short, integer and double). This includes implementation of multivariate sparse lin-
79 ear models, Principal Component Analysis, matrix operations, and numerical summaries. The
80 statistical tools developed in bigstatsr can be used for other types of data as long as they can
81 be represented as matrices. Package bigsnpr depends on bigstatsr, using a special type of FBM
82 object to store the genotypes, called “FBM.code256”. Package bigsnpr implements algorithms
83 which are specific to the analysis of SNP arrays, such as calls to external software for process-
84 ing steps, I/O (Input/Output) operations from binary PLINK files, and data analysis operations
85 on SNP data (thinning, testing, plotting). We use both a real case-control genomic dataset for
86 Celiac disease and large-scale simulated data to illustrate application of the two R packages,
87 including association study and computation of Polygenic Risk Scores. We also compare re-
88 sults from the two R packages with those obtained when using PLINK and EIGENSOFT, and
89 report execution times along with the code to perform major computational tasks.

3 Methods

3.1 Memory-mapped files

The two R packages don't use standard read operations on a file nor load the genotype matrix entirely in memory. They use an hybrid solution: memory-mapping. Memory-mapping is used to access data, possibly stored on disk, as if it were in memory. This solution is made available within R through the BH package, providing access to Boost C++ Header Files¹.

We are aware of the software library SNPFile that uses memory-mapped files to store and efficiently access genotype data, coded in C++ (Nielsen and Mailund 2008) and of the R package BEDMatrix² which provides memory-mapping directly for binary PLINK files. With the two packages we developed, we made this solution available in R and in C++ via package Rcpp (Eddelbuettel and François 2011). The major advantage of manipulating genotype data within R, almost as it were a standard matrix in memory, is the possibility of using most of the other tools that have been developed in R (R Core Team 2017). For example, we provide sparse multivariate linear models and an efficient algorithm for Principal Component Analysis (PCA) based on adaptations from R packages biglasso and RSpectra (Qiu and Mei 2016; Zeng and Breheny 2017).

Memory-mapping provides transparent and faster access than standard read/write operations. When an element is needed, a small chunk of the genotype matrix, containing this element, is accessed in memory. When the system needs more memory, some chunks of the matrix are freed from the memory in order to make space for others. All this is managed by the Operating System so that it is seamless and efficient. It means that if the same chunks of data are used repeatedly, it will be very fast the second time they are accessed, the third time and so on. Of course, if the memory size of the computer is larger than the size of the dataset, the file could fit entirely in memory and every second access would be fast.

¹<http://www.boost.org/>

²<https://github.com/QuantGen/BEDMatrix>

114 **3.2 Data management, preprocessing and imputation**

115 Package bigsnpr currently takes as input a variety of formats (e.g. vcf, bed/bim/fam, ped/map).
116 However, it uses PLINK for conversion to bed/bim/fam format and for Quality Control (QC) of
117 the data, so that we first provide R functions that use system calls to PLINK for the conversion
118 and QC steps (Figure 1). Then, fast read/write operations from/to bed/bim/fam PLINK files are
119 implemented. PLINK files are then read into a “bigSNP” object, which contains the genotype
120 Filebacked Big Matrix (FBM), a data frame with information on samples and another data
121 frame with information on SNPs. We also provide another function which could be used to
122 read from tabular-like text files in order to create a genotype in the format “FBM”.

123 We developed a special FBM object, called “FBM.code256”, that can be used to seam-
124 lessly store up to 256 arbitrary different values, while having a relatively efficient storage.
125 Indeed, each element is stored on one byte which requires 8 times less disk storage than double-
126 precision numbers but 4 times more space than the binary PLINK format “.bed”. With these 256
127 values, the matrix can store genotype calls and missing values (4 values), best guess genotypes
128 (3 values) and genotype dosages (likelihoods) rounded to two decimal places (201 values).

129 We also provide two functions for imputing missing values of genotyped SNPs (Figure 2).
130 The first function is a wrapper to PLINK and Beagle (Browning and Browning 2008) which
131 takes bed files as input and return bed files without missing values, and should therefore be used
132 before reading the data in R. The second function is a new algorithm we developed in order to
133 have a fast imputation method without losing much of imputation accuracy. This algorithm is
134 based on Machine Learning approaches for genetic imputation (Wang *et al.* 2012) and doesn't
135 use phasing, thus allowing for a dramatic decrease in computation time. It only relies on some
136 local XGBoost models. XGBoost is an optimized distributed gradient boosting library that can
137 be used in R and provides some of the best results in machine learning competitions (Chen and
138 Guestrin 2016). XGBoost builds decision trees that can detect nonlinear interactions, partially
139 reconstructing phase, making it well suited for imputing genotype matrices. Systematically,
140 for each SNP, we provide an estimation of imputation error by separating non-missing data
141 into training/test sets. The training set is used to build a model for predicting missing data. The
142 prediction model is then evaluated on the test set for which we know the true genotype values,

143 which gives an unbiased estimator of the number of genotypes that have been wrongly imputed
144 for that particular SNP.

145 **3.3 Population structure and SNP thinning based on Linkage Dis-** 146 **equilibrium**

147 For computing Principal Components (PCs) of a large-scale genotype matrix, we provide sev-
148 eral functions related to SNP thinning and two functions, for computing a partial Singular Value
149 Decomposition (SVD), one based on eigenvalue decomposition, `big_SVD`, and the other on
150 randomized projections, `big_randomSVD` (Figure 3). While the function based on eigenvalue
151 decomposition is at least quadratic in the smallest dimension, the function based on random-
152 ized projections runs in linear time in all dimensions (Lehoucq and Sorensen 1996). Pack-
153 age `bigstatsr` use the same PCA algorithm as `FlashPCA2` called Implicitly Restarted Arnoldi
154 Method (IRAM), which is implemented in R package `RSpectra`. The main difference between
155 the two implementations is that `FlashPCA2` computes vector-matrix multiplications with the
156 genotype matrix based on the binary PLINK file whereas `bigstatsr` computes these multiplica-
157 tions based on the FBM format, which enables parallel computations and easier subsetting.

158 SNP thinning improves ascertainment of population structure with PCA (Abdellaoui *et al.*
159 2013). There are at least 3 different approaches to thin SNPs based on Linkage Disequilibrium,
160 two of them named pruning and clumping, address SNPs in LD close to each others because
161 of recombination events, while the third one address long-range regions with a complex LD
162 pattern due to other biological events such as inversions (Price *et al.* 2008). First, pruning, the
163 most naive approach, is an algorithm that sequentially scan the genome for nearby SNPs in LD,
164 performing pairwise thinning based on a given threshold of correlation. A variant of pruning
165 is clumping. Clumping is useful if a statistic is available to sort the SNPs by importance, e.g.
166 association with a phenotype, and for discarding SNPs in LD with a more associated SNP
167 relatively to the phenotype of interest. Furthermore, we advise to always use clumping instead
168 of pruning (by using the minor allele frequency as the statistic of importance, which is the
169 default) because, in some particular cases, pruning can leave regions of the genome without

170 any representative SNP at all³.

171 As mentioned above, the third approach that is generally combined with pruning or clump-
172 ing consists of removing SNPs in long-range LD regions (Price *et al.* 2008). Long-range LD
173 regions for the human genome are available as an online table that our packages can use to
174 discard SNPs in long-range LD regions while computing PCs⁴. However, the pattern of LD
175 might be population specific, so we developed an algorithm that automatically detects these
176 regions and removes them. This algorithm consists in the following steps: first, PCA is per-
177 formed using a subset of SNP remaining after clumping, then outliers SNPs are detected using
178 Mahalanobis distance as implemented in the R package pcadapt (Luu *et al.* 2017). Finally,
179 the algorithm considers that consecutive outlier SNPs are in long-range LD regions. Indeed,
180 a long-range LD region would cause SNPs in this region to have strong consecutive weights
181 (loadings) in the PCA. This algorithm is implemented in function `snp_autoSVD` and will be
182 referred by this name in the rest of the paper.

183 3.4 Association tests and Polygenic Risk Scores

Any test statistic that is based on counts could be easily implemented because we provide fast counting summaries. Among these tests, the Armitage trend test and the MAX3 test statistic are already provided for binary outcome (Zheng *et al.* 2012). We also implement statistical tests based on linear and logistic regressions. For the linear regression, for each SNP j , a t-test is performed on $\beta^{(j)}$ where

$$\hat{y} = \alpha^{(j)} + \beta^{(j)}SNP^{(j)} + \gamma_1^{(j)}PC_1 + \dots + \gamma_K^{(j)}PC_K + \delta_1^{(j)}COV_1 + \dots + \delta_K^{(j)}COV_L,$$

and K is the number of principal components and L is the number of other covariates (such as the age and gender). Similarly, for the logistic regression, for each SNP j , a Z-test is performed on $\beta^{(j)}$ where

$$\log \frac{\hat{p}}{1 - \hat{p}} = \alpha^{(j)} + \beta^{(j)}SNP^{(j)} + \gamma_1^{(j)}PC_1 + \dots + \gamma_K^{(j)}PC_K + \delta_1^{(j)}COV_1 + \dots + \delta_K^{(j)}COV_L,$$

³<https://goo.gl/T5SJqM>

⁴<https://goo.gl/8TngVE>

184 and $\hat{p} = \mathbb{P}(Y = 1)$ and Y denotes the binary phenotype.

185 The R packages also implement functions to compute Polygenic Risk Scores using two ap-
186 proaches. The first method is the widely-used Pruning + Thresholding (P+T) model based on
187 univariate GWAS summary statistics as described in previous equations. Under the P+T model,
188 a coefficient of regression is learned independently for each SNP along with a corresponding
189 p-value. The SNPs are first clumped (P) so that there remains only SNPs that are weakly cor-
190 related with each other. Thresholding (T) consists in removing SNPs that are under a certain
191 level of significance (P-value threshold to be determined). A polygenic risk score is defined
192 as the sum of allele counts of the remaining SNPs weighted by the corresponding regression
193 coefficients (Chatterjee *et al.* 2013; Dudbridge 2013; Golan and Rosset 2014). The second
194 approach doesn't use univariate summary statistics but instead train a multivariate model on
195 all the SNPs and covariables at once, optimally accounting for correlation between predictors
196 (Abraham *et al.* 2012). The currently available models are linear and logistic regressions and
197 Support Vector Machine (SVM). These models include lasso and elastic-net regularizations,
198 which reduce the number of predictors (SNPs) included in the predictive models (Friedman
199 *et al.* 2010; Tibshirani 1996; Zou and Hastie 2005). Package bigstatsr provides a fast imple-
200 mentation of these models by using efficient rules to discard most of the predictors (Tibshirani
201 *et al.* 2012). The implementation of these algorithms is based on modified versions of functions
202 available in the R packages sparseSVM and biglasso (Zeng and Breheny 2017). These modi-
203 fications allow to include covariates in the models and to use these algorithms on the special
204 type of FBM called "FBM.code256" used in bigsnpr.

205 **3.5 Data analyzed**

206 In this paper, two datasets are analyzed: the celiac disease cohort and the POPRES datasets
207 (Dubois *et al.* 2010; Nelson *et al.* 2008). The Celiac dataset is composed of 15,283 individuals
208 of European ancestry genotyped on 295,453 SNPs. The POPRES dataset is composed of 1385
209 individuals of European ancestry genotyped on 447,245 SNPs. For computation times compar-
210 ison, we replicated individuals in the Celiac dataset 5 and 10 times in order to increase sample
211 size while keeping the same population structure and pattern of Linkage Disequilibrium as the

212 original dataset. To assess scalability of our algorithms for a biobank-scale genotype dataset,
213 we formed another dataset of 500,000 individuals and 1 million SNPs, also through replication
214 of the Celiac dataset.

215 **3.6 Reproducibility**

216 All the code used in this paper along with results, such as execution times and figures, are
217 available as HTML R notebooks in the Supplementary Data.

218 **4 Results**

219 **4.1 Overview**

220 We present the results for three different analyses. First, we illustrate the application of R
221 packages `bigstatsr` and `bigsnpr`. Secondly, we compare the performance of the R packages
222 to the performance obtained with PLINK and FastPCA (EIGENSOFT). Thirdly, we present
223 results of the two new methods implemented in these packages, one method for the automatic
224 detection and removal of long-range LD regions in PCA and another for the imputation of
225 missing genotypes. We use three types of data: a case-control cohort for the celiac disease,
226 the European population cohort POPRES and simulated datasets using real genotypes from the
227 Celiac cohort. We compare performances on two computers, a desktop computer with 64GB
228 of RAM and 12 cores (6 physical cores), and a laptop with only 8GB of RAM and 4 cores (2
229 physical cores). For the functions that enable parallelism, we use half of the cores available on
230 the corresponding computer.

231 **4.2 Application**

232 We performed an association study and computed a polygenic risk score for the Celiac cohort.
233 The data was preprocessed following steps from figure 1, removing individuals and SNPs which
234 had more than 5% of missing values, non-autosomal SNPs, SNPs with a minor allele frequency
235 lower than 0.05 or a p-value for the Hardy-Weinberg exact test lower than 10^{-10} , and finally,

236 removing the first individual in each pair of individuals with a proportion of alleles shared
237 IBD greater than 0.08 (Purcell *et al.* 2007). For the POPRES dataset, this resulted in 1382
238 individuals and 344,614 SNPs with no missing value. For the Celiac dataset, this resulted in
239 15,155 individuals and 281,122 SNPs with an overall genotyping rate of 99.96%. The 0.04%
240 missing genotype values were imputed with the XGBoost method. If we used a standard R
241 matrix to store the genotypes, this data would require 32GB of memory. On the disk, the
242 “.bed” file requires 1GB and the “.bk” file (storing the FBM) requires 4GB.

243 We used `bigstatsr` and `bigsnpr` R functions to compute the first Principal Components (PCs)
244 of the Celiac genotype matrix and to visualize them (Figure 4). We then performed a Genome-
245 Wide Association Study (GWAS) investigating how Single Nucleotide Polymorphisms (SNPs)
246 are associated with the celiac disease, while adjusting for PCs, and plotted the results as a
247 Manhattan plot (Figure 5). As illustrated in the supplementary data, the whole pipeline is user-
248 friendly and requires only 20 lines of R code.

249 To illustrate the scalability of the two R packages, we performed a GWAS analysis on 500K
250 individuals and 1M SNPs. The GWAS analysis completed in approximately 11 hours using the
251 aforementioned desktop computer. The GWAS analysis was composed of four main steps.
252 First we read from PLINK files in our format "bigSNP" in 1 hour. Then, we removed SNPs
253 in long-range LD regions and used SNP clumping, leaving 93,083 SNPs in 5.4h. Then, the 10
254 first PCs were computed on the 500K individuals and these remaining SNPs in 1.8h. Finally,
255 we performed a linear association test on the complete 500K dataset for each of the 1M SNPs,
256 using the 10 first PCs as covariables in 2.9h.

257 **4.3 Method Comparison**

258 We first compared the GWAS and PRS computations obtained with the R packages to the ones
259 obtained with PLINK 1.9 and EIGENSOFT 6.1.4. For most functions, multithreading is not
260 available yet in PLINK, nevertheless, PLINK-specific algorithms that use bitwise parallelism
261 (e.g. pruning) are still faster than the parallel algorithms reimplemented in package `bigsnpr`
262 (Table 1). Overall, the computations with our two R packages for an association study and a
263 polygenic risk score are of the same order of magnitude as when using PLINK and EIGEN-

264 SOFT (Tables 1 and 2). However, the whole analysis pipeline makes use of R calls only; there
265 is no need to write temporary files and functions have parameters which enable subsetting of
266 the genotype matrix without having to copy it.

267 On our desktop computer, we compared the computation times of FastPCA, FlashPCA2
268 to the similar function `big_randomSVD` implemented in `bigstatsr`. For each comparison, we
269 used the 93,083 SNPs which were remaining after pruning and we computed 10 PCs. We
270 used the datasets of growing size simulated from the Celiac dataset. Overall, our function
271 `big_randomSVD` showed to be almost twice as fast as FastPCA and FlashPCA2 and 8 times
272 as fast when using parallelism (an option not currently possible with either FastPCA or Flash-
273 PCA2) with 6 cores (Figure 6). We also compared results in terms of precision by comparing
274 squared correlation between approximated PCs and “true” PCs provided by an exact singular
275 value decomposition obtained with SmartPCA. FastPCA, FlashPCA2 and `bigstatsr` infer the
276 true first 6 PCs but the squared correlation between true PCs and approximated ones decreases
277 for larger PCs when using FastPCA (Fast mode of EIGENSOFT) whereas it remains larger
278 than 0.999 when using FlashPCA2 or `bigstatsr` (Figure 7).

279 **4.4 Automatic detection of long-range LD regions**

280 For the detection of long-range LD regions during the computation of PCA, we tested the
281 function `snp_autoSVD` on both the Celiac and POPRES datasets. For the POPRES dataset,
282 the algorithm converged in two iterations. The first iterations found 3 long-range LD regions
283 in chromosomes 2, 6 and 8 (Table S1). We compared the PCs of genotypes obtained after
284 applying `snp_autoSVD` with the PCs obtained after removing pre-determined long-range LD
285 regions⁵ and found a mean correlation of 89.6% between PCs, mainly due to a rotation of PC7
286 and PC8 (Table S2). For the Celiac dataset, we found 5 long-range LD regions (Table S3) and
287 a mean correlation of 98.6% between PCs obtained with `snp_autoSVD` and the ones obtained
288 by clumping with removing of predetermined long-range LD regions (Table S4).

289 For the Celiac dataset, we further compared results of PCA obtained when using `snp_autoSVD`
290 and when computing PCA without removing any long range LD region (only clumping at

⁵<https://goo.gl/8TngVE>

291 $R^2 > 0.2$). When not removing any long range LD region, we show that PC4 and PC5
292 don't capture population structure and correspond to a long-range LD region in chromosome
293 8 (Figures S1 and S2). When automatically removing some long-range LD regions with
294 `snp_autoSVD`, we show that PC4 and PC5 reflect population structure (Figure S1). Moreover,
295 loadings are more equally distributed among SNPs after removal of long-range LD regions
296 (Figure S2). This is confirmed by Gini coefficients (measure of dispersion) of each squared
297 loadings that are significantly smaller when computing SVD with `snp_autoSVD` than when no
298 long-range LD region is removed (Figure S3).

299 **4.5 Imputation of missing values for genotyped SNPs**

300 For the imputation method based on XGBoost, we compared the imputation accuracy and com-
301 putation times with Beagle on the POPRES dataset. The histogram of the minor allele frequen-
302 cies (MAFs) of this dataset is provided in figure S4 and there is no missing value. We used a
303 Beta-binomial distribution to simulate the number of missing values by SNP and then randomly
304 introduced missing values according to these numbers, resulting in approximately 3% of miss-
305 ing values overall (Figure S5). Imputation was compared between function `snp_fastImpute` of
306 package `bigsnpr` and Beagle 4.1 (version of January 21, 2017). Overall, `snp_fastImpute` made
307 4.7% of imputation errors whereas Beagle made only 3.1% of errors but it took Beagle 14.6
308 hours to complete while our method only took 42 minutes (20 times less). We also show that
309 the estimation of the number of imputation errors is accurate (Figure S6). For the Celiac dataset
310 in which there was already missing values, in order to further compare computation times, we
311 report that `snp_fastImpute` took less than 10 hours to complete for the whole genome whereas
312 Beagle didn't finish imputing chromosome 1 in 48 hours.

313 **5 Discussion**

314 We have developed two R packages, `bigstatsr` and `bigsnpr`, which enable multiple analyses of
315 large-scale genotype datasets in a single comprehensive framework. Linkage Disequilibrium
316 pruning, Principal Component Analysis, association tests and computations of polygenic risk

317 scores are made available in this software. Implemented algorithms are both fast and memory-
318 efficient, allowing the use of laptops or desktop computers to make genome-wide analyses.
319 Technically, `bigstatsr` and `bigsnpr` could handle any size of datasets. However, if the OS has
320 to often swap between the file and the memory for accessing the data, this would slow down
321 data analysis. For example, the Principal Component Analysis (PCA) algorithm in `bigstatsr` is
322 iterative so that the matrix has to be sequentially accessed over a hundred times. If the num-
323 ber of samples times the number of SNPs remaining after pruning is larger than the available
324 memory, this slowdown would happen. For instance, a 32GB computer would be slow when
325 computing PCs on more than 100K samples and 300K SNPs remaining after LD thinning.

326 The two R packages use a matrix-like format, which makes it easy to develop new func-
327 tions in order to experiment and develop new ideas. Integration in R makes it possible to take
328 advantage of the vast and diverse R libraries. For example, we developed a fast and accurate
329 imputation algorithm for genotyped SNPs using the widely-used machine learning algorithm
330 XGBoost available in the R package `xgboost`. Other functions, not presented here, are also
331 available and all the functions available within the package `bigstatsr` are not specific to SNP
332 arrays, so that they could be used for other omic data or in other fields of research.

333 We think that the two R packages and the corresponding data format could help researchers
334 to develop new ideas and algorithms to analyze genome-wide data. For example, we wish to
335 use these packages to train much more accurate predictive models than the standard P+T model
336 currently in use when computing Polygenic Risk Scores. As a second example, multiple impu-
337 tation has been shown to be a very promising method for increasing statistical power of a GWAS
338 (Palmer and Pe'er 2016), and it could be implemented with the data format “FBM.code256”
339 without having to write multiple files.

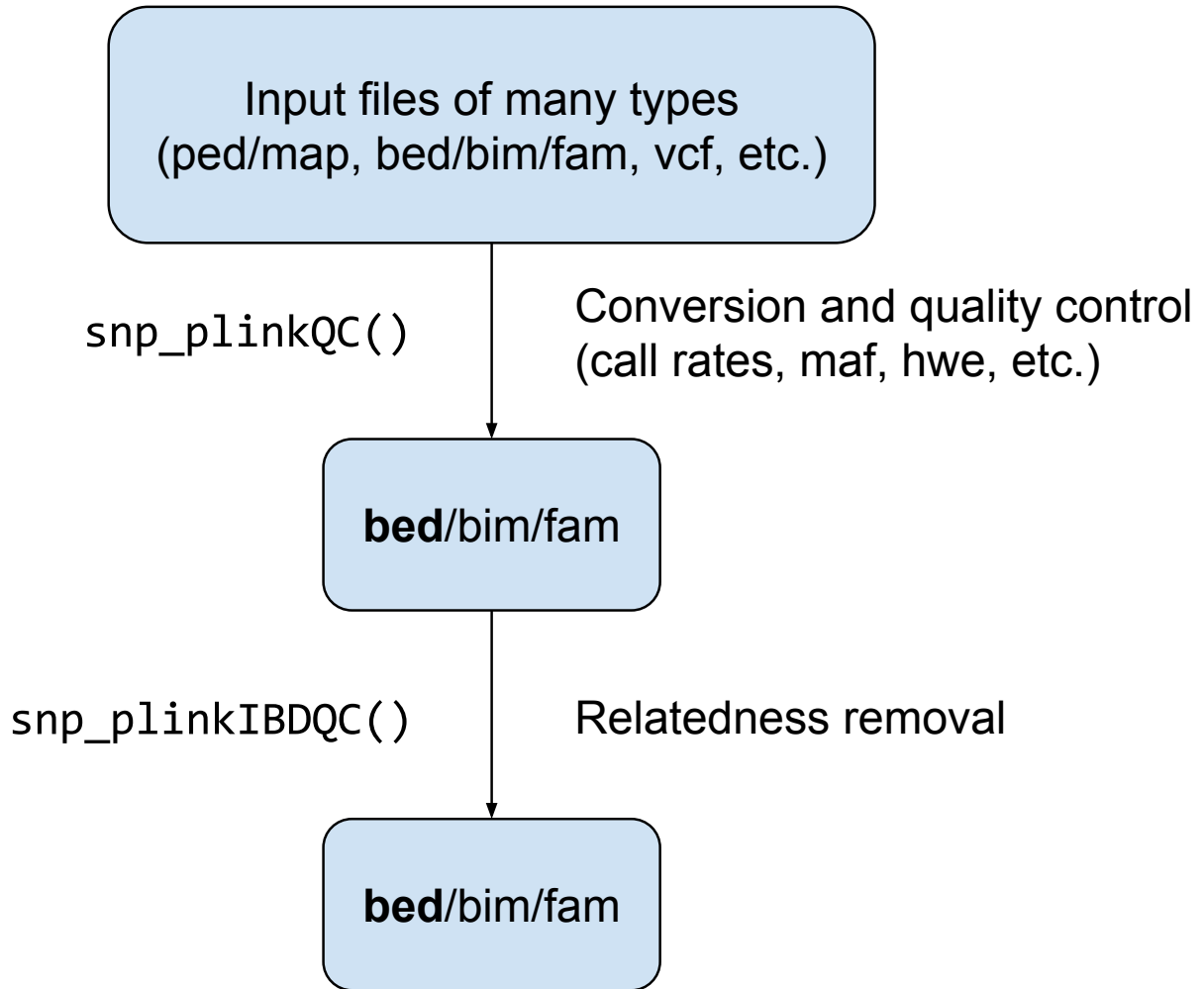


Figure 1: Conversion and Quality Control preprocessing functions available in package bigsnpr via system calls to PLINK.

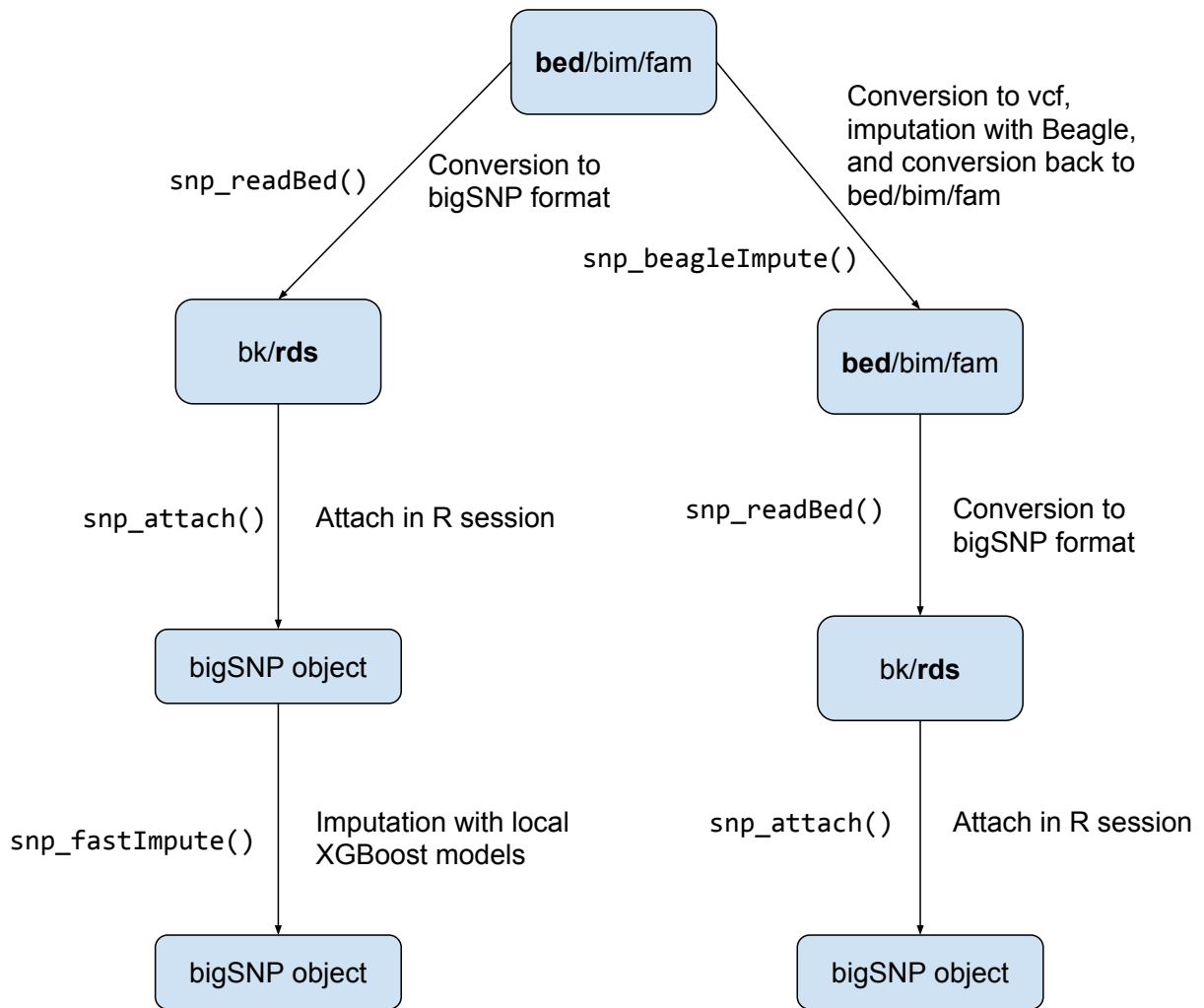


Figure 2: Imputation and reading functions available in package `bigsnpr`.

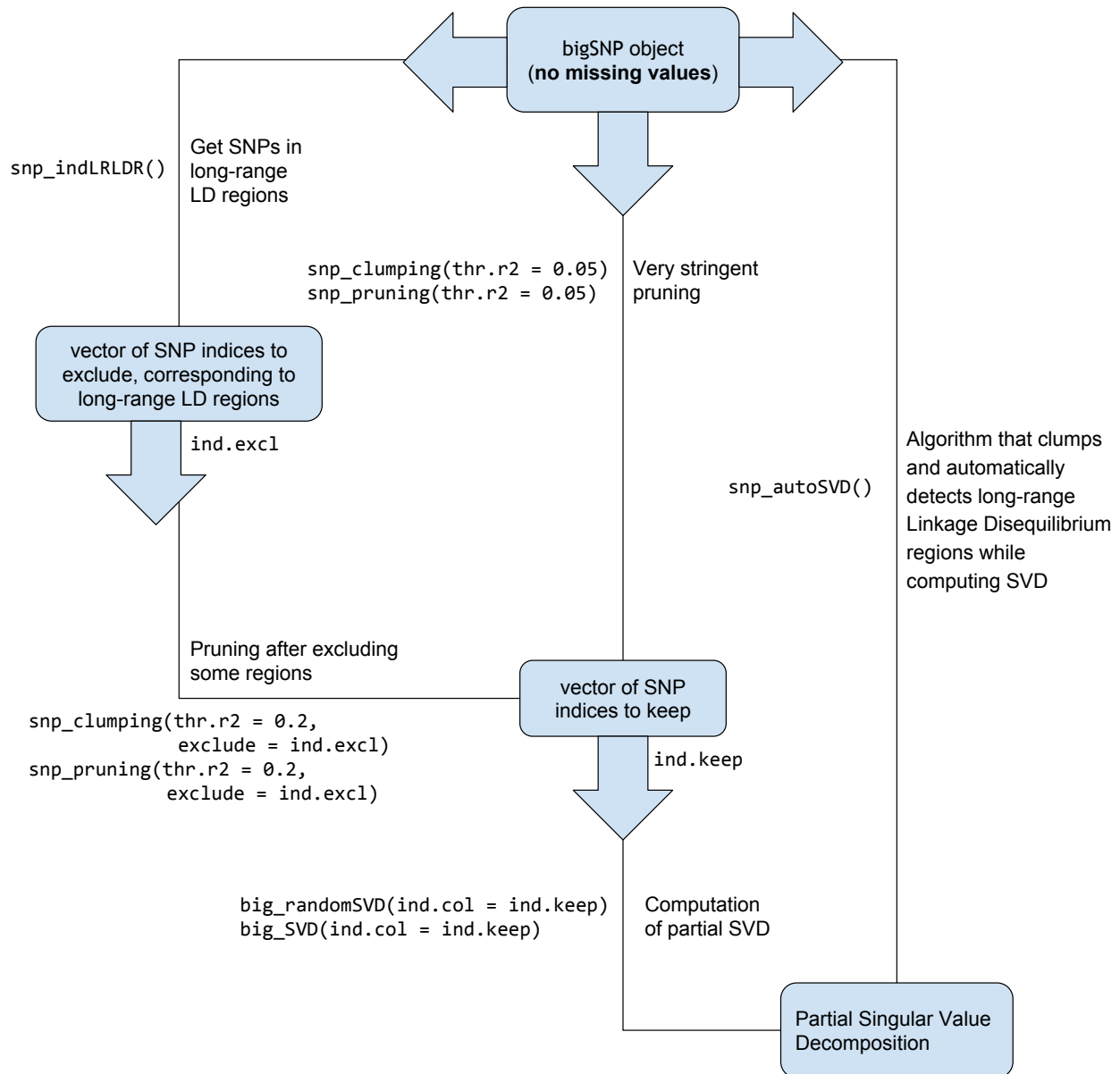


Figure 3: Functions available in packages bigstatsr and bigsnpr for the computation of a partial Singular Value Decomposition of a genotype array, with 3 different methods for thinning SNPs.

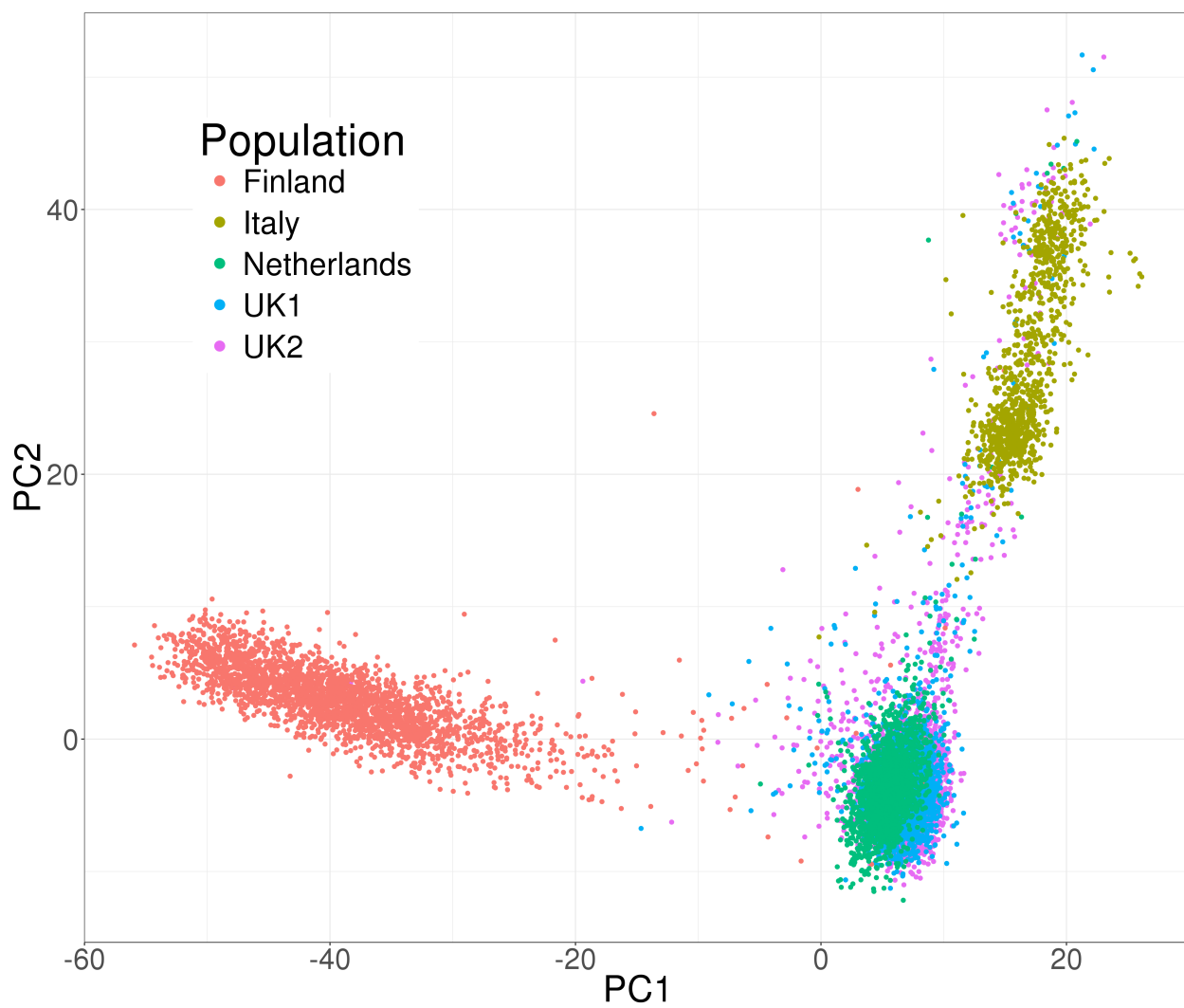


Figure 4: Principal Components of the celiac cohort genotype matrix produced by package bigstatsr.

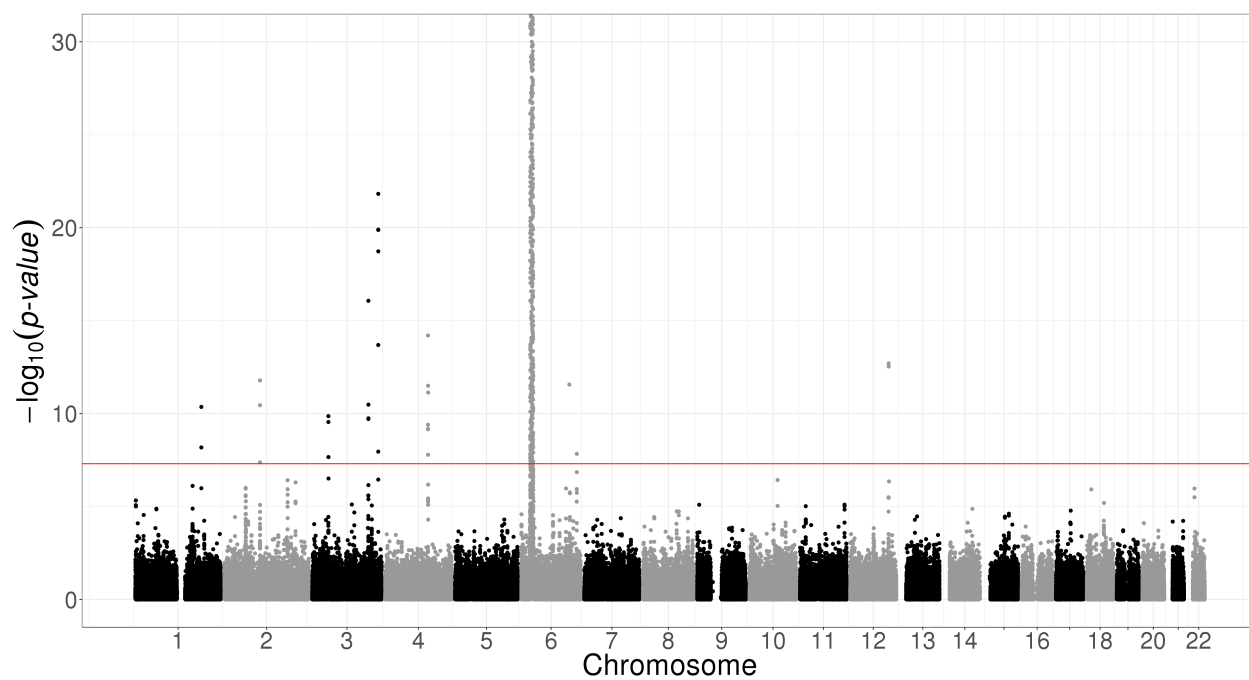


Figure 5: Manhattan plot of the celiac disease cohort produced by package bigsnpr. Some SNPs in chromosome 6 have p-values smaller than the 10^{-30} threshold used for visualization purposes.

Operation	Execution times (in seconds)	
	PLINK and FastPCA	bigstatsr and bigsnpr
Reading PLINK files	n/a	5 / 20
Pruning	4 / 4	14 / 52
Computing 10 PCs	306 / 315	58 / 180
GWAS (binary phenotype)	339 / 293	301 / 861
Total	649 / 612	378 / 1113

Table 1: Execution times with bigstatsr and bigsnpr compared to PLINK and FastPCA for making a GWAS for the Celiac dataset. The first execution time is with a desktop computer (6 cores used and 64GB of RAM) and the second one is with a laptop computer (2 cores used and 8GB of RAM).

Operation	Execution times (in seconds)	
	PLINK	bigstatsr and bigsnpr
GWAS (binary phenotype)	232 / 239	178 / 650
Clumping	49 / 58	10 / 35
PRS	9 / 10	2 / 3
Total	290 / 307	190 / 688

Table 2: Execution times with bigstatsr and bigsnpr compared to PLINK and FastPCA for making a PRS for a training set of 80% of the Celiac dataset. The first execution time is with a desktop computer (6 cores used and 64GB of RAM) and the second one is with a laptop computer (2 cores used and 8GB of RAM).

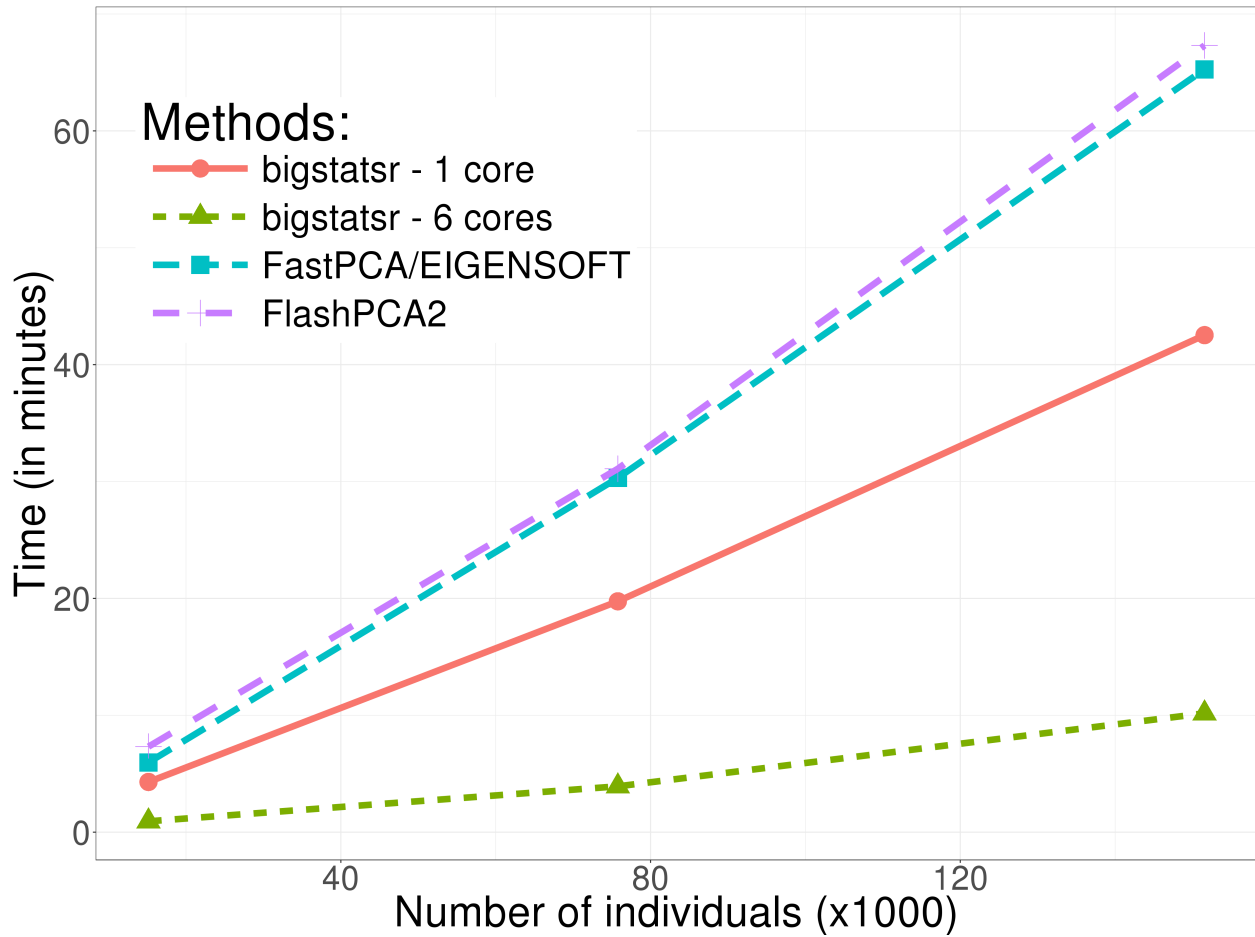


Figure 6: Benchmark comparisons between randomized Partial Singular Value Decomposition available in FlashPCA2, FastPCA (fast mode of SmartPCA/EIGENSOFT) and package bigstatsr. It shows the computation time in minutes as a function of the number of samples. The first 10 principal components have been computed based on the 93,083 SNPs which remained after thinning.

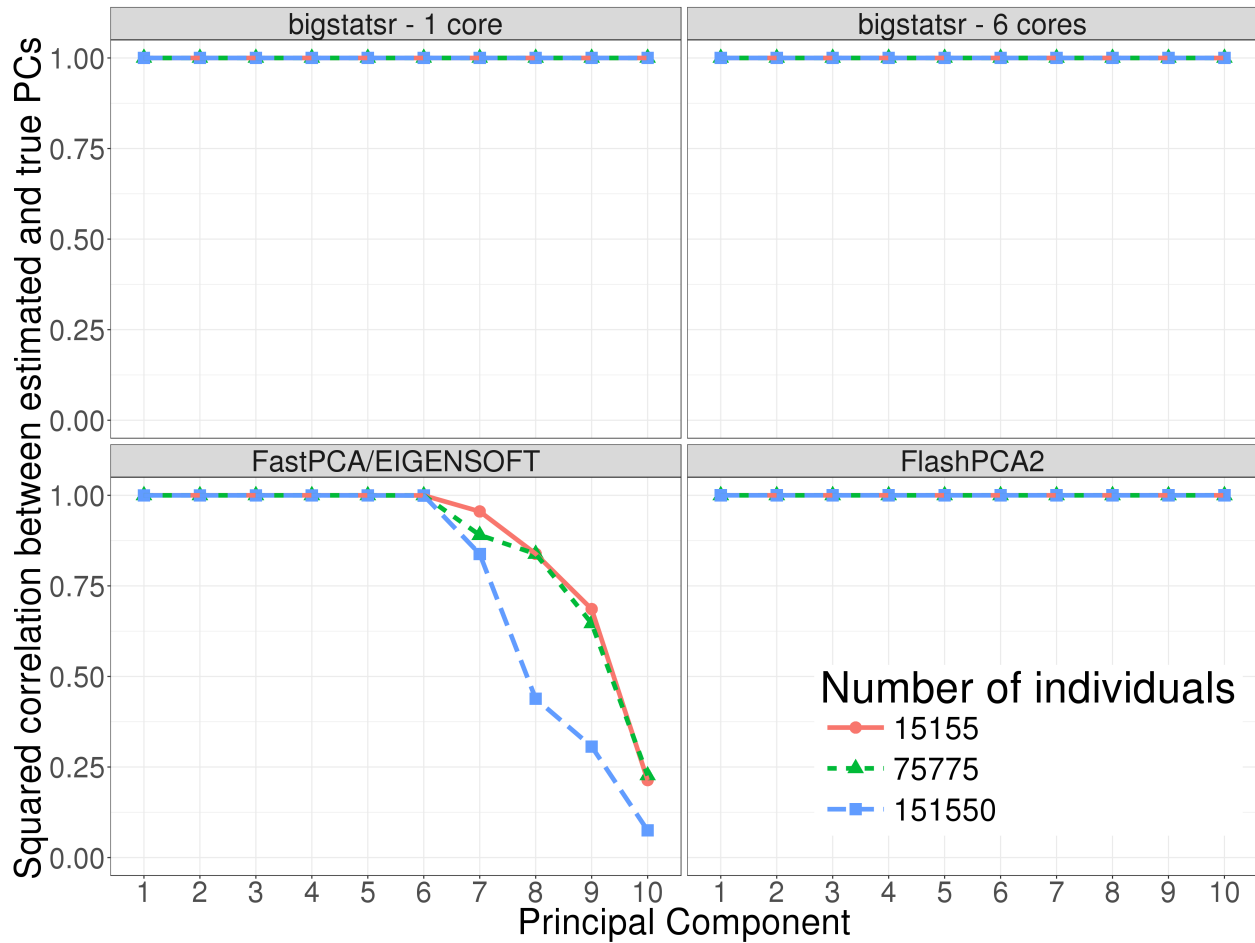


Figure 7: Precision comparisons between randomized Partial Singular Value Decomposition available in FlashPCA2, FastPCA (fast mode of SmartPCA/EIGENSOFT) and package bigstatsr. It shows the squared correlation between approximated PCs and “true” PCs (given by the slow mode of SmartPCA) of the Celiac dataset (whose individuals have been repeated 1, 5 and 10 times).

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422

Supplementary Data

423

5.1 Long-range LD regions

Chromosome		Start (Mb)	Stop (Mb)
1	2	134.7 (134.5)	137.3 (138)
2	6	27.5 (25.5)	33.1 (33.5)
3	8	6.6 (8)	13.2 (12)

Table S1: Regions found by `snp_autoSVD` for the POPRES dataset. Numbers in parentheses correspond to regions referenced in Price *et al.* (2008).

	PC1	PC2	PC3	PC4	PC5	PC6	PC7	PC8	PC9	PC10
PC1	100.0	-0.1	-0.0	0.1	-0.1	0.0	0.0	0.0	-0.0	-0.0
PC2	0.1	100.0	-0.0	0.1	-0.0	-0.0	-0.0	0.2	-0.1	-0.0
PC3	0.0	-0.0	99.9	0.9	0.1	-0.1	-0.3	0.2	0.4	0.1
PC4	-0.1	-0.1	-0.9	99.7	-1.0	0.7	0.6	0.2	0.3	0.9
PC5	0.1	0.0	-0.1	1.1	99.3	1.3	-0.8	1.3	-4.2	-2.4
PC6	-0.0	0.0	0.1	-0.7	-1.0	97.7	-3.5	6.1	7.9	-6.2
PC7	-0.0	-0.1	0.2	-0.3	-1.7	0.3	58.3	73.2	-25.9	9.1
PC8	0.1	-0.1	-0.3	0.4	-0.5	-5.3	-73.5	59.5	15.8	13.2
PC9	0.0	0.1	-0.4	-0.8	5.0	-7.6	27.8	11.0	91.9	9.0
PC10	0.1	0.0	0.0	-0.9	1.6	10.2	3.9	-19.6	-6.3	89.2

Table S2: Correlation between scores of PCA for the POPRES dataset when automatically removing long-range LD regions and when removing them based on a predefined table.

Chromosome		Start (Mb)	Stop (Mb)
1	2	134.4 (134.5)	138.1 (138)
2	6	23.8 (25.5)	35.8 (33.5)
3	8	6.3 (8)	13.5 (12)
4	3	163.1 (n/a)	164.9 (n/a)
5	14	46.6 (n/a)	47.5 (n/a)

Table S3: Regions found by `snp_autoSVD` for the celiac dataset. Numbers in parentheses correspond to regions referenced in Price *et al.* (2008).

	PC1	PC2	PC3	PC4	PC5	PC6	PC7	PC8	PC9	PC10
PC1	100.0	-0.1	-0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
PC2	0.1	100.0	0.0	0.0	-0.0	-0.0	0.0	-0.0	-0.0	-0.0
PC3	0.1	-0.0	99.9	0.2	-0.0	0.1	0.1	0.1	0.0	-0.1
PC4	-0.0	-0.0	-0.3	99.9	-0.1	0.1	-0.1	0.0	0.1	0.1
PC5	0.0	0.0	0.0	0.1	99.7	0.9	-0.3	0.1	-0.8	-0.6
PC6	-0.0	0.0	-0.1	-0.2	-0.8	99.6	0.5	-0.5	-0.2	-0.4
PC7	-0.0	0.0	-0.1	0.0	0.5	-0.4	98.9	3.1	0.7	1.6
PC8	0.0	0.0	-0.2	-0.0	-0.2	0.5	-3.2	98.4	-4.5	-1.5
PC9	-0.0	-0.0	-0.0	0.0	0.6	0.1	-0.7	4.6	96.9	-10.7
PC10	-0.0	-0.0	0.1	-0.1	0.3	0.1	-1.2	1.5	8.6	92.7

Table S4: Correlation between scores of PCA for the Celiac dataset when automatically removing long-range LD regions and when removing them based on a predefined table.

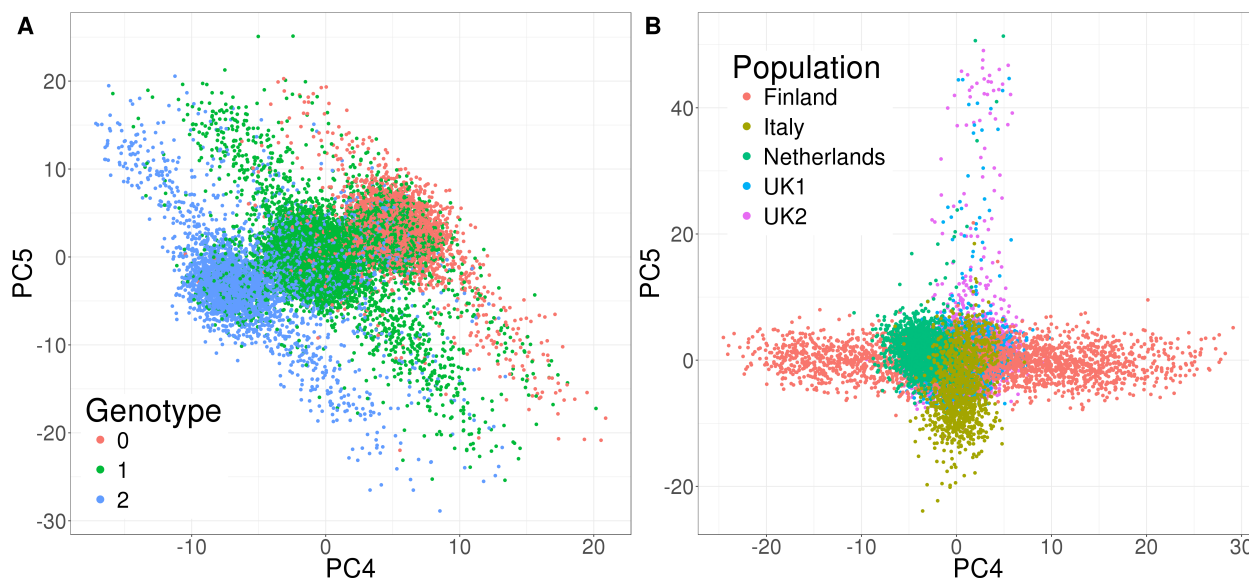


Figure S1: PC4 and PC5 of the celiac disease dataset. Left panel, PC scores obtained without removing any long range LD region (only clumping at $R^2 > 0.2$). Individuals are coloured according to their genotype at the SNP that has the highest loading for PC4. Right panel, PC scores obtained with the automatic detection and removal of long-range LD regions. Individuals are coloured according to their population of origin.

5.2 Imputation

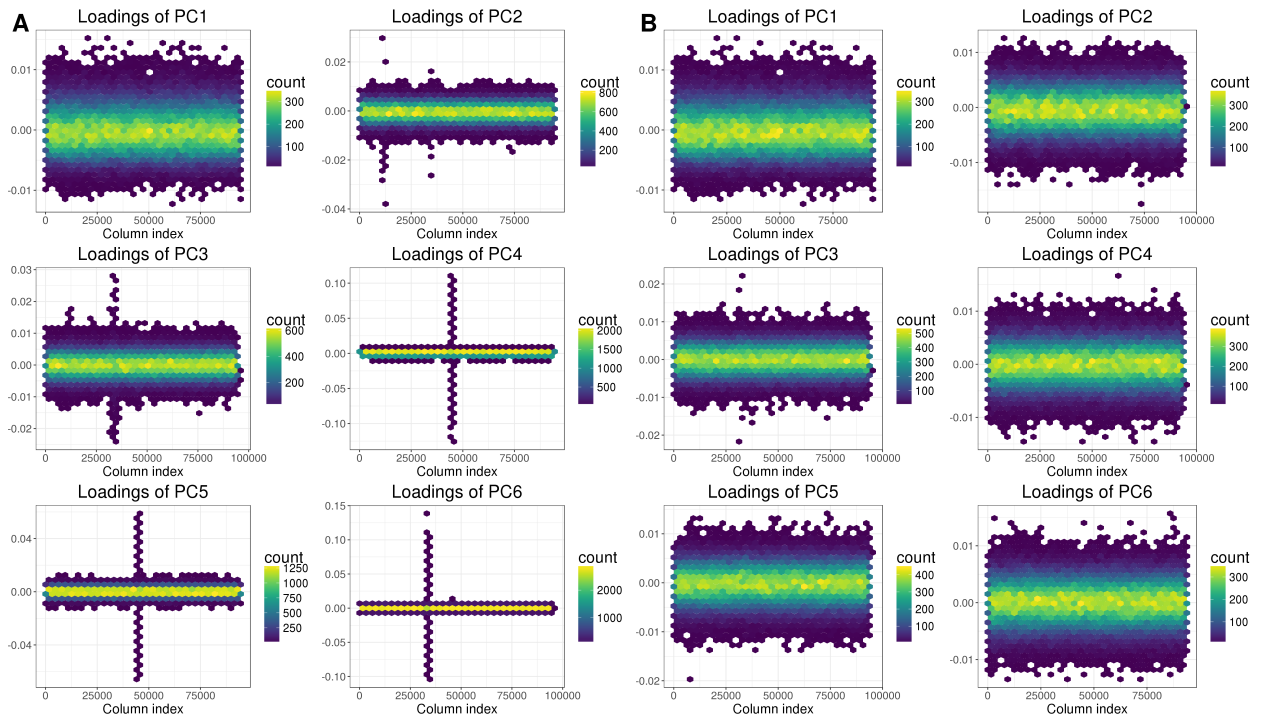


Figure S2: Loadings of first 6 PCs of the celiac disease dataset plotted as hexbins (2-D histogram with hexagonal cells). On the left, without removing any long range LD region (only clumping at $R^2 > 0.2$). On the right, with the automatic detection and removal of long-range LD regions.

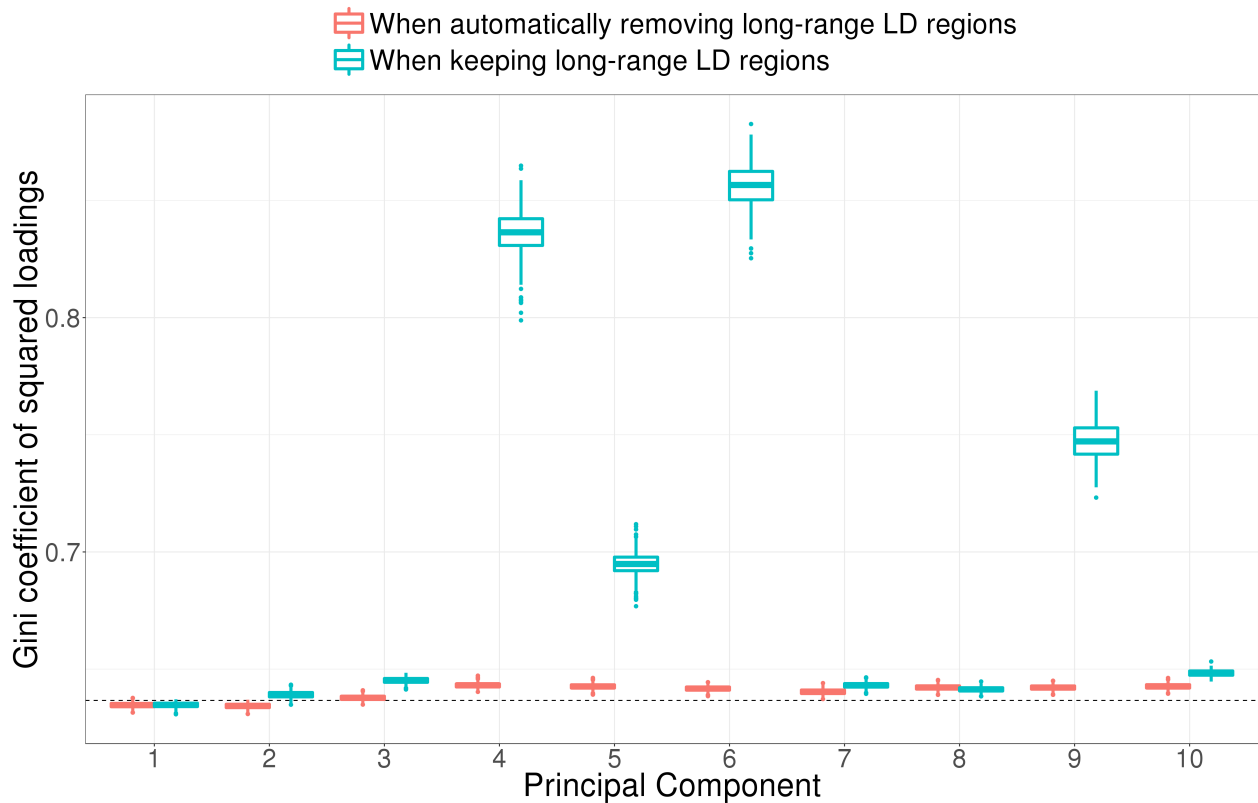


Figure S3: Boxplots of 1000 bootstrapped Gini coefficients (measure of statistical dispersion) of squared loadings without removing any long range LD region (only clumping at $R^2 > 0.2$) and with the automatic detection and removal of long-range LD regions. The dashed line corresponds to the theoretical value for gaussian loadings.

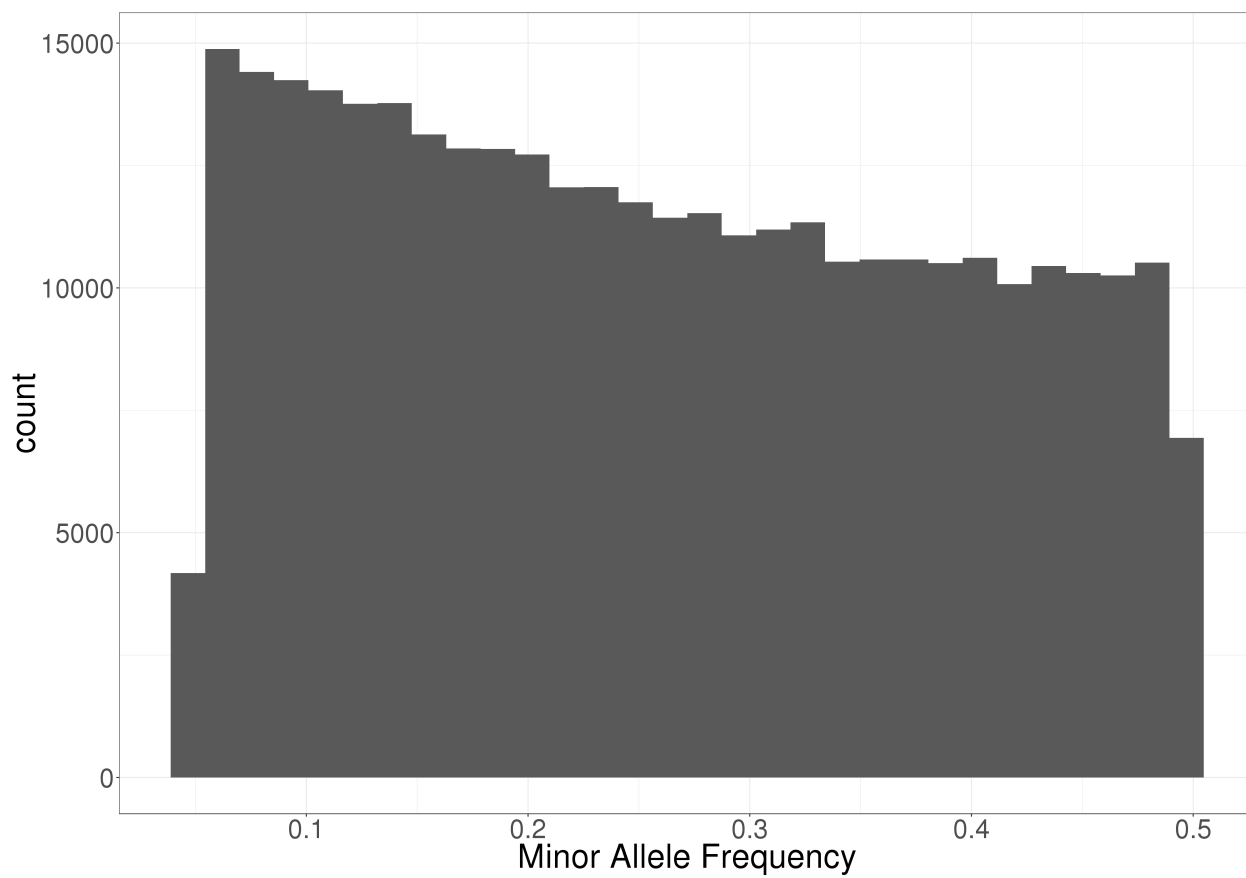


Figure S4: Histogram of the minor allele frequencies of the POPRES dataset used for comparing imputation methods.

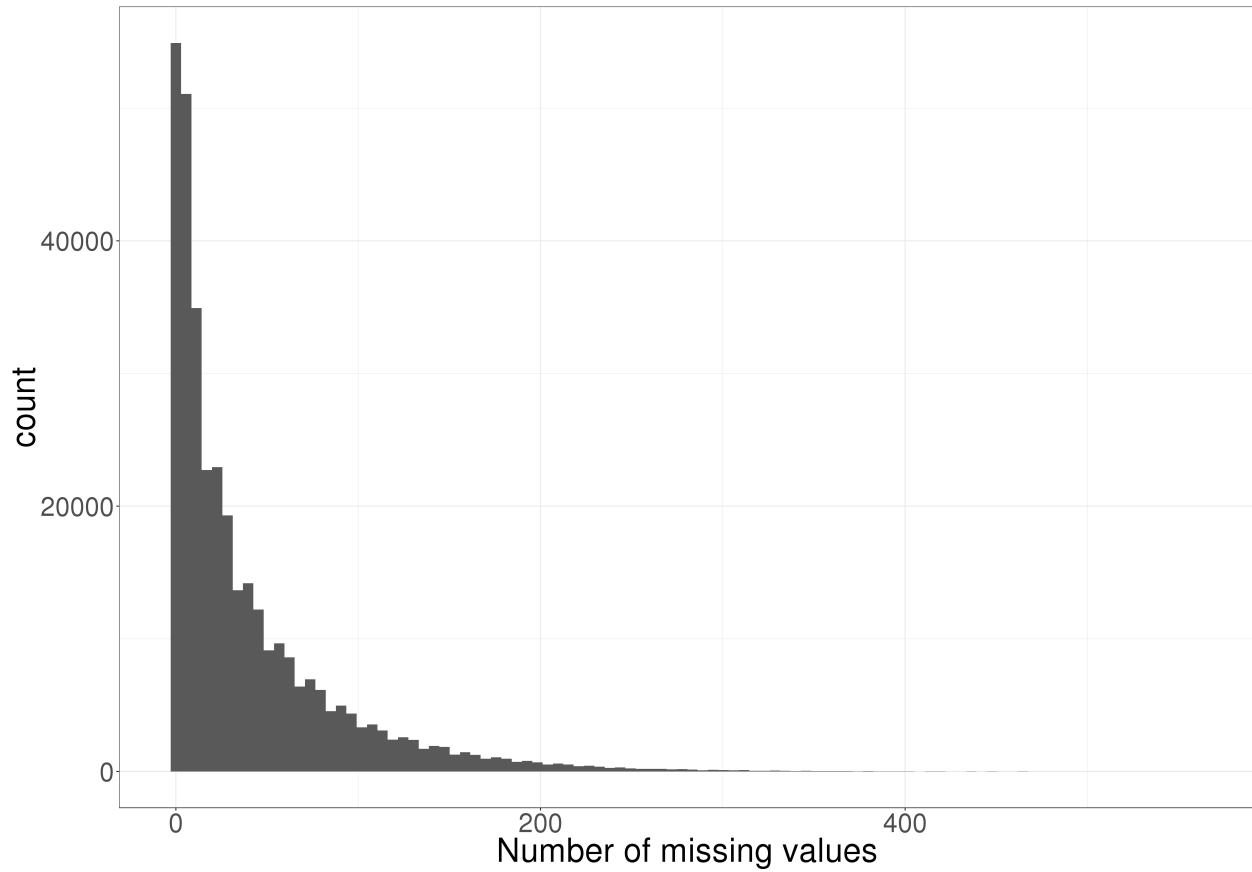


Figure S5: Histogram of the number of missing values by SNP. These numbers were generated using a Beta-binomial distribution.

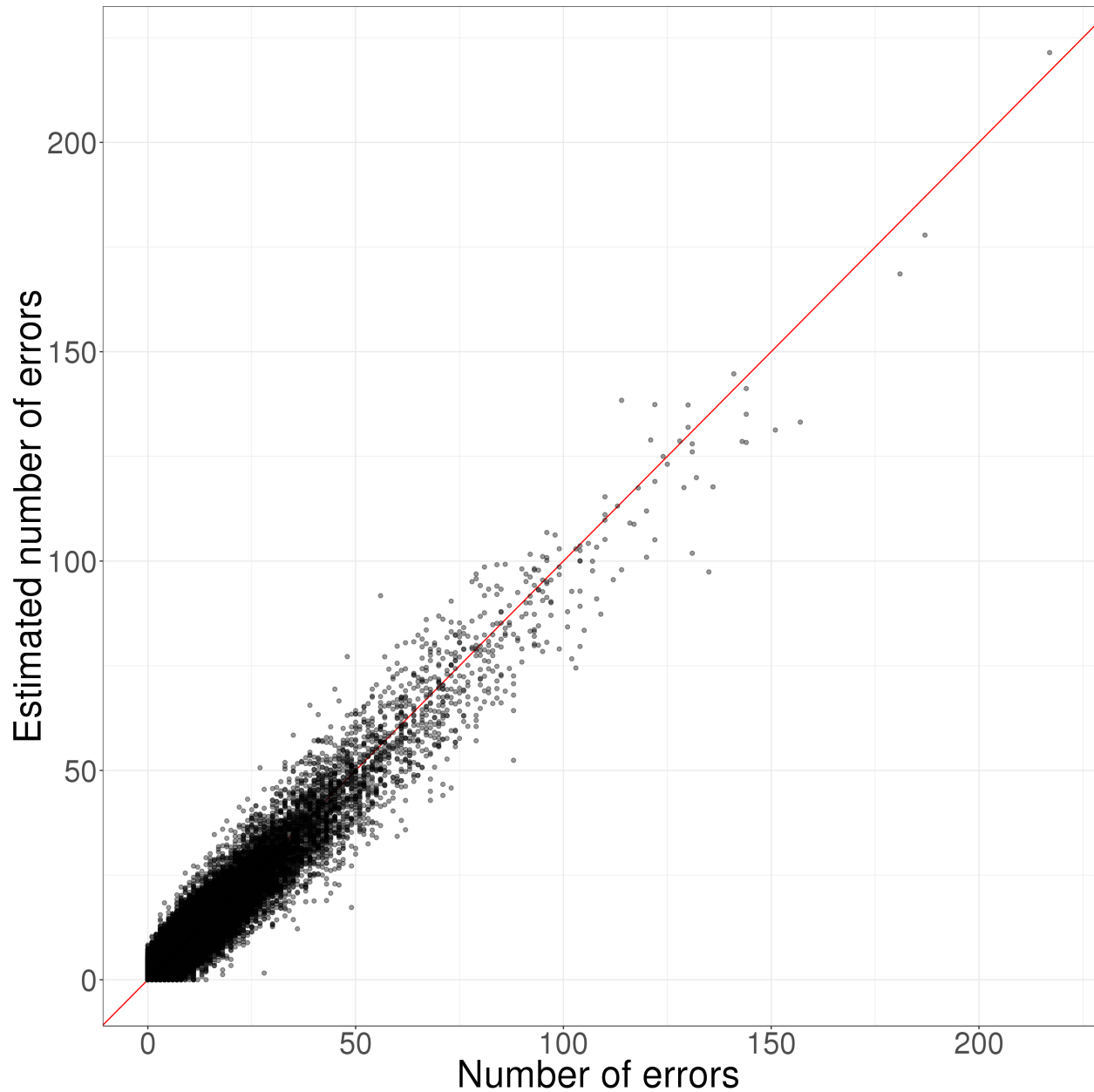


Figure S6: Number of imputation errors vs the estimated number of imputation errors by SNP. For each SNP with missing data, the number of imputation errors corresponds to the number of individuals for which imputation is incorrect. The estimated number of errors is a quantity that is returned when imputing with `snp_fastimpute`, which is based on XGBoost (Chen and Guestrin 2016).