RAREsim Vignette

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This vigette describes how to use the RAREsim R package to simulate rare variant genetic data.

The example below simulates a one cM block on chromosome 19. Here, RAREsim simulates haplotypes to match target data from the African ancestry group from gnomAD v2.1 (Karczewski, et al., 2020).

## Install the package

library(RAREsim)

The source code for all functions within the RAREsim package can be found at <https://github.com/meganmichelle/RAREsim>. The package currently must be downloaded through github using devtools.

RAREsim has three main steps: (1) simulate genetic data with an abundance of rare variants using [HAPGEN2](https://mathgen.stats.ox.ac.uk/genetics_software/hapgen/hapgen2.html) (Su, 2011), (2) estimate the expected number of variants in MAC bins, and (3) probabilistically prune the rare variants to match the estimated number of variants in each MAC bin.

An example simulation with HAPGEN2 can be found on the [RAREsim Example Code github page](https://github.com/meganmichelle/RAREsim_Example). By simulating with default parameters and input haplotypes with information at all sequencing bases, including monomorphic sites, HAPGEN2 simulates an abundance of rare variants.

In order to emulate real sequencing data, RAREsim prunes the simulated variants by returning all or a subset of alternate alleles back to reference. In order to prune, RAREsim first estimates the expected number of variants within MAC bins. The number of variants in each MAC bin can either estimated using default parameters, modifying default parameters, or fitting target data. If the exact sample size of observed sequencing data is to be simulated, the observed data can be matched directly.

## The Number of Variants function

For a given region, the *Number of Variants* function estimates the number of variants per Kb, , for a sample size . Estimating the number of variants can be achieved by 1) Fitting target data to estimate parameters, 2) Using default parameters, or 3) directly inputting parameters to the function. Additionally, a user may directly input the number of variants expected in the region (e.g. 1000 variants).

#### 1) Fitting Target Data

Target data is used to estimate and to optimize the function to fit the target data.

The Number of Variants target data consists of various sample sizes () and the observed number of variants per Kb in the region of interest. Ancestry specific data is advised. Data should be formatted with the first column as the number of individuals () and the second column as the observed number of variants per Kb in the region of interest ().

Here we will fit the example data for the African ancestry population. Example data is available in the R package for each of the four ancestries: African (AFR), East Asian (EAS), Non-Finnish European (NFE), and South Asian (SAS).

# load the target data  
data("nvariant\_afr")  
print(nvariant\_afr, row.names = FALSE)

## n per\_kb  
## 10 0.2627568  
## 20 0.6831678  
## 50 1.5239897  
## 100 2.7326712  
## 200 4.3092123  
## 500 7.6199485  
## 1000 12.1919176  
## 2000 19.3914551  
## 3070 25.2246571  
## 5000 33.4226707  
## 5040 33.7905302  
## 8128 45.1941773

The target data is used to estimate and within a least squares loss function, optimizing using sequential quadratic programming (SQP). This optimization is implemented via the *Fit\_nvariant* function.

nvar <- Fit\_nvariant(nvariant\_afr)  
nvar

## $phi  
## [1] 0.1638108  
##   
## $omega  
## [1] 0.6248848

The output of the *Fit\_nvariant* function are the parameters phi () and omega (), respectively. The estimated parameters can then be used to determine the expected number of variants per Kb within the region of interest, given the number of individuals to be simulated, .

For example, to simulate the sample size observed in the target data, (), we calculate . This can be done with the *nvariant* function.

Parameter values for phi (), omega (), and the sample size (n) found previously are used here.

nvariant(phi = nvar$phi, omega = nvar$omega, N = 8128)

## [1] 45.46027

#### 2) Using Default Parameters

RAREsim also provides ancestry specific default parameters for phi (), omega (). To use the default parameters, the ancestry must be specified: African (AFR), East Asian (EAS), Non-Finnish European (NFE), or South Asian (SAS).

nvariant(N=8128, pop = 'AFR')

## [1] 43.66395

#### 3) Directly Inputting Parameters

Finally, parameters can be directly input into the *Number of Variants* function.

nvariant(phi = 0.1638108, omega = 0.6248848, N = 8128)

## [1] 45.46026

### Total Number of Variants in the Region

The example data here is a cM block with 19,029 bp. Thus, to calculate the total expected number of variants in the region, we multiple the expected number of variants per Kb (*Nvariant*) by 19.029.

19.029\*nvariant(phi = 0.1638108, omega = 0.6248848, N = 8128)

## [1] 865.0633

## The Allele Frequency Spectrum (AFS) Function

The *AFS* function inputs a MAC (*z*) and outputs the proportion of variants at MAC = z, (). This is done by estimating and to optimize the function . Here *b* ensures that the sum of the individual rare allele count proportions equals the total proportion of rare variants, .

The *AFS* function inputs a data frame with the upper and lower boundaries for each bin and proportion of variants within each respective bin. The default bins used here and within the evaluation of RAREsim are:

MAC = 1  
MAC = 2  
MAC = 3 - 5  
MAC = 6 - 10  
MAC = 11 - 20  
MAC = 21 - MAF = 0.5%  
MAC = 0.5% - MAF = 1%

Estimating the AFS can be achieved by 1) Fitting target data to estimate parameters, 2) Using default parameters, or 3) directly inputting parameters to the function. Additionally, a user may directly input the proportion of variants in each MAC bin.

#### 1) Fitting Target Data

Below is an example of the AFS target data for the African ancestry group. The first two columns identify the lower and upper boundaries of each MAC bin. The third column specifies the observed proportion of variants within each MAC bin in the target data.

# load the data  
data("afs\_afr")  
colnames(afs\_afr)[3] <- 'Prop'  
print(afs\_afr)

## Lower Upper Prop  
## 1 1 1 0.50257998  
## 2 2 2 0.16305470  
## 3 3 5 0.08255934  
## 4 6 10 0.05882353  
## 5 11 20 0.03715170  
## 6 21 81 0.05675955  
## 7 82 162 0.01754386

To fit the *AFS* function (*Fit\_afs*), RAREsim requires the data frame with MAC bins and proportion of variants (shown above), the number of subjects to simulate , and the total proportion of rare variants, . Here, we will simulate the sample size observed in gnomAD, . The function estimates the parameters alpha (), beta (), and , and includes the estimated proportion of variants based on calculations from the fitted parameters, as shown below.

af <- Fit\_afs(Observed\_bin\_props = afs\_afr)  
print(af)

## $alpha  
## [1] 1.594622  
##   
## $beta  
## [1] -0.2846474  
##   
## $b  
## [1] 0.297495  
##   
## $Fitted\_results  
## Lower Upper Prop  
## 1 1 1 0.50753380  
## 2 2 2 0.12582725  
## 3 3 5 0.12226962  
## 4 6 10 0.06152310  
## 5 11 20 0.04187244  
## 6 21 81 0.04709594  
## 7 82 162 0.01235050

#### 2) Using Default Parameters

As with the *Variants per Kb* function, default parameters can be used to estimate the parameters for the *AFS* function with the *AFS\_calc* function. As the default parameters are ancestry specific, the ancestry needs to be specified as pop = AFR, EAS, NFE, or SAS when default parameters are used. The parameters alpha (), beta (), and b can be specified, or default parameters can be used. Both implementations of the function require a MAC bin dataframe, with the bins specified.

This is the first two columns of the AFS target data.

mac <- afs\_afr[,c(1:2)]

Using the MAC bins as input and specifying an African ancestry, the default parameters are used below to estimate the proportion of variants within each bin.

afs(mac\_bins = mac, pop = 'AFR')

## Lower Upper Prop  
## 1 1 1 0.51573550  
## 2 2 2 0.12461241  
## 3 3 5 0.12033906  
## 4 6 10 0.06047216  
## 5 11 20 0.04122759  
## 6 21 81 0.04658283  
## 7 82 162 0.01229418

#### 3) Directly Inputting Parameters

The afs function can inputs the parameters alpha, beta, and b, along with the MAC bin endpoints.

afs(alpha = 1.594622, beta = -0.2846474, b = 0.297495, mac\_bins = mac)

## Lower Upper Prop  
## 1 1 1 0.50753386  
## 2 2 2 0.12582721  
## 3 3 5 0.12226954  
## 4 6 10 0.06152304  
## 5 11 20 0.04187238  
## 6 21 81 0.04709586  
## 7 82 162 0.01235047

## Expected Number of Variants per MAC bin

Using the parameter estimates from the *Number of Variants* and *AFS* functions, the expected number of variants in each MAC bin can be estimated. An example using the total number of varants and estimated proportion of variants per MAC bin is shown below.

bin\_estimates <- Expected\_variants(Total\_num\_var = 865.0633, mac\_bin\_prop = af$Fitted\_results)  
print(bin\_estimates)

## Lower Upper Expected\_var  
## 1 1 1 439.04886  
## 2 2 2 108.84854  
## 3 3 5 105.77096  
## 4 6 10 53.22138  
## 5 11 20 36.22231  
## 6 21 81 40.74097  
## 7 82 162 10.68396

The output of the *Expected\_variants* function is the exected number of variants in each MAC bin within the simulation region. This output (shown above) is input for the pruning function.

The *Number of Variants* and *AFS* function can also be calculated within the *Expected\_variants* function.

bin\_estimates <- Expected\_variants(Total\_num\_var = 19.029\*nvariant(phi = 0.1638108, omega = 0.6248848, N = 8128), mac\_bin\_prop = afs(mac\_bins = mac, pop = 'AFR'))  
print(bin\_estimates)

## Lower Upper Expected\_var  
## 1 1 1 446.14384  
## 2 2 2 107.79762  
## 3 3 5 104.10090  
## 4 6 10 52.31224  
## 5 11 20 35.66447  
## 6 21 81 40.29710  
## 7 82 162 10.63524

## Pruning Variants

In order to use RAREsim to prune simulated data, genetic data must be simulated with HAPGEN2 with all sequencing bases, including monomorphic variants, added to the input haplotypes. HAPGEN2 will simulate an abudance of rare variants to allow for variant pruning. Additionally, a MAC file (count of the number of alternate alleles at each bp) enables an efficient and fast pruning process. It is recommended to create the MAC file within the process of simulating data with HAPGEN2, as shown in the example code that is available on the [RAREsim Example code github page](https://github.com/meganmichelle/RAREsim_Example).

Below is an example MAC file created from the haplotypes simulated for the African ancestry group and the region of interest. Each row represents one bp in the haplotype file.

data("MAC\_afr")

Pruning happens in two stages: 1) RAREsim theoretically decides which variants should be pruned and 2) Prunes the haplotype and legend files

#### 1) Theoretically Prune

Pruning variants requires a MAC file from the simulated data and the expected number of variants within each MAC bin (product of the *Expected\_variants* function).

ToPrune <- Pruning\_info(MAC = MAC\_afr, expected = bin\_estimates)  
head(ToPrune, row.names = FALSE)

## $ToRemove  
## line Current\_mac New\_mac  
## 382 382 137 0  
## 569 569 108 0  
## 2060 2060 117 0  
## 3856 3856 93 0  
## 4575 4575 103 0  
## 5314 5314 147 0  
## 9713 9713 140 0  
## 12816 12816 127 0  
## 15209 15209 91 0  
## 15685 15685 113 0  
## 16406 16406 133 0  
## 18690 18690 101 0  
## 53 53 22 0  
## 212 212 44 0  
## 337 337 26 0  
## 391 391 30 0  
## 399 399 45 0  
## 422 422 29 0  
## 515 515 52 0  
## 570 570 28 0  
## 599 599 28 0  
## 615 615 21 0  
## 645 645 74 0  
## 646 646 30 0  
## 703 703 21 0  
## 853 853 27 0  
## 1067 1067 64 0  
## 1114 1114 32 0  
## 1279 1279 22 0  
## 1707 1707 23 0  
## 1792 1792 35 0  
## 1885 1885 24 0  
## 1908 1908 30 0  
## 1913 1913 27 0  
## 1966 1966 25 0  
## 2253 2253 23 0  
## 2298 2298 45 0  
## 2536 2536 52 0  
## 2897 2897 24 0  
## 2946 2946 38 0  
## 3032 3032 22 0  
## 3127 3127 22 0  
## 3128 3128 31 0  
## 3175 3175 33 0  
## 3319 3319 23 0  
## 3557 3557 22 0  
## 3600 3600 30 0  
## 3636 3636 55 0  
## 3742 3742 27 0  
## 3989 3989 22 0  
## 4005 4005 23 0  
## 4032 4032 33 0  
## 4384 4384 23 0  
## 4485 4485 21 0  
## 4629 4629 65 0  
## 4667 4667 27 0  
## 4830 4830 24 0  
## 4869 4869 71 0  
## 4940 4940 26 0  
## 5004 5004 27 0  
## 5060 5060 21 0  
## 5079 5079 30 0  
## 5089 5089 30 0  
## 5215 5215 23 0  
## 5307 5307 79 0  
## 5380 5380 30 0  
## 5500 5500 22 0  
## 5648 5648 21 0  
## 5668 5668 24 0  
## 5760 5760 31 0  
## 5798 5798 31 0  
## 5823 5823 31 0  
## 5871 5871 28 0  
## 5897 5897 22 0  
## 5898 5898 23 0  
## 5978 5978 40 0  
## 6161 6161 21 0  
## 6222 6222 23 0  
## 6333 6333 65 0  
## 6414 6414 41 0  
## 6459 6459 34 0  
## 6500 6500 25 0  
## 6576 6576 37 0  
## 6647 6647 31 0  
## 6793 6793 44 0  
## 6805 6805 25 0  
## 6887 6887 81 0  
## 6897 6897 21 0  
## 6910 6910 34 0  
## 6965 6965 32 0  
## 7014 7014 42 0  
## 7153 7153 29 0  
## 7362 7362 74 0  
## 7628 7628 22 0  
## 7677 7677 24 0  
## 7771 7771 24 0  
## 7846 7846 31 0  
## 7913 7913 32 0  
## 8025 8025 74 0  
## 8080 8080 21 0  
## 8145 8145 24 0  
## 8178 8178 41 0  
## 8278 8278 24 0  
## 8401 8401 60 0  
## 8408 8408 43 0  
## 8419 8419 64 0  
## 8575 8575 24 0  
## 8680 8680 30 0  
## 8727 8727 58 0  
## 8811 8811 43 0  
## 8815 8815 21 0  
## 8831 8831 72 0  
## 8914 8914 41 0  
## 9030 9030 28 0  
## 9075 9075 40 0  
## 9092 9092 24 0  
## 9592 9592 23 0  
## 9636 9636 23 0  
## 9652 9652 26 0  
## 9688 9688 42 0  
## 9700 9700 24 0  
## 9707 9707 21 0  
## 9757 9757 56 0  
## 9814 9814 26 0  
## 9841 9841 21 0  
## 10058 10058 34 0  
## 10128 10128 38 0  
## 10263 10263 33 0  
## 10550 10550 25 0  
## 10859 10859 37 0  
## 10881 10881 45 0  
## 11065 11065 37 0  
## 11147 11147 51 0  
## 11536 11536 71 0  
## 11543 11543 26 0  
## 11913 11913 29 0  
## 12036 12036 48 0  
## 12051 12051 24 0  
## 12127 12127 31 0  
## 12147 12147 29 0  
## 12178 12178 40 0  
## 12289 12289 41 0  
## 12293 12293 40 0  
## 12312 12312 31 0  
## 12389 12389 29 0  
## 12433 12433 26 0  
## 12450 12450 25 0  
## 12469 12469 23 0  
## 12511 12511 41 0  
## 12577 12577 21 0  
## 12682 12682 22 0  
## 12800 12800 78 0  
## 12826 12826 23 0  
## 12838 12838 35 0  
## 12850 12850 42 0  
## 12870 12870 26 0  
## 12936 12936 40 0  
## 13197 13197 30 0  
## 13198 13198 72 0  
## 13285 13285 53 0  
## 13348 13348 71 0  
## 13367 13367 21 0  
## 13721 13721 22 0  
## 13737 13737 23 0  
## 13821 13821 52 0  
## 13867 13867 47 0  
## 13914 13914 53 0  
## 14083 14083 23 0  
## 14110 14110 53 0  
## 14133 14133 22 0  
## 14283 14283 24 0  
## 14289 14289 74 0  
## 14329 14329 28 0  
## 14354 14354 32 0  
## 14425 14425 24 0  
## 14436 14436 25 0  
## 14499 14499 46 0  
## 14582 14582 45 0  
## 14678 14678 29 0  
## 14692 14692 25 0  
## 14716 14716 48 0  
## 14822 14822 28 0  
## 14972 14972 25 0  
## 15068 15068 32 0  
## 15081 15081 24 0  
## 15143 15143 32 0  
## 15413 15413 22 0  
## 15486 15486 40 0  
## 15584 15584 55 0  
## 15697 15697 34 0  
## 15710 15710 36 0  
## 15907 15907 24 0  
## 16028 16028 57 0  
## 16848 16848 53 0  
## 16906 16906 21 0  
## 16913 16913 64 0  
## 17011 17011 23 0  
## 17384 17384 35 0  
## 17386 17386 24 0  
## 17406 17406 23 0  
## 17418 17418 36 0  
## 17422 17422 42 0  
## 17485 17485 24 0  
## 17565 17565 21 0  
## 17597 17597 36 0  
## 17605 17605 38 0  
## 17616 17616 30 0  
## 17647 17647 24 0  
## 17667 17667 25 0  
## 17696 17696 25 0  
## 17748 17748 33 0  
## 17759 17759 49 0  
## 17786 17786 28 0  
## 17888 17888 40 0  
## 17968 17968 51 0  
## 18048 18048 64 0  
## 18145 18145 44 0  
## 18236 18236 31 0  
## 18324 18324 49 0  
## 18333 18333 43 0  
## 18464 18464 60 0  
## 18573 18573 51 0  
## 18601 18601 44 0  
## 18861 18861 37 0  
## 18909 18909 25 0  
## 19 19 18 0  
## 78 78 16 0  
## 109 109 11 0  
## 144 144 11 0  
## 247 247 13 0  
## 543 543 15 0  
## 588 588 20 0  
## 718 718 11 0  
## 787 787 14 0  
## 882 882 11 0  
## 1105 1105 20 0  
## 1109 1109 19 0  
## 1182 1182 14 0  
## 1183 1183 12 0  
## 1303 1303 13 0  
## 1373 1373 14 0  
## 1449 1449 13 0  
## 1453 1453 19 0  
## 1467 1467 11 0  
## 1501 1501 13 0  
## 1553 1553 16 0  
## 1617 1617 12 0  
## 1646 1646 20 0  
## 1748 1748 18 0  
## 1837 1837 18 0  
## 1872 1872 11 0  
## 1890 1890 18 0  
## 1969 1969 20 0  
## 1980 1980 20 0  
## 2024 2024 19 0  
## 2107 2107 11 0  
## 2194 2194 11 0  
## 2285 2285 11 0  
## 2320 2320 13 0  
## 2361 2361 14 0  
## 2366 2366 16 0  
## 2406 2406 13 0  
## 2432 2432 11 0  
## 2493 2493 19 0  
## 2541 2541 15 0  
## 2677 2677 11 0  
## 2735 2735 13 0  
## 2755 2755 12 0  
## 2803 2803 13 0  
## 2924 2924 13 0  
## 3010 3010 18 0  
## 3041 3041 18 0  
## 3142 3142 16 0  
## 3217 3217 16 0  
## 3264 3264 14 0  
## 3331 3331 12 0  
## 3365 3365 17 0  
## 3366 3366 15 0  
## 3418 3418 17 0  
## 3433 3433 15 0  
## 3451 3451 12 0  
## 3551 3551 17 0  
## 3609 3609 17 0  
## 3703 3703 15 0  
## 3748 3748 15 0  
## 3788 3788 19 0  
## 3835 3835 13 0  
## 3839 3839 14 0  
## 3947 3947 15 0  
## 3961 3961 18 0  
## 4026 4026 17 0  
## 4048 4048 12 0  
## 4066 4066 15 0  
## 4205 4205 15 0  
## 4218 4218 19 0  
## 4229 4229 16 0  
## 4238 4238 13 0  
## 4261 4261 13 0  
## 4359 4359 12 0  
## 4362 4362 11 0  
## 4385 4385 11 0  
## 4475 4475 11 0  
## 4548 4548 12 0  
## 4554 4554 17 0  
## 4570 4570 20 0  
## 4624 4624 19 0  
## 4645 4645 18 0  
## 4653 4653 12 0  
## 4663 4663 12 0  
## 4717 4717 19 0  
## 4781 4781 15 0  
## 4787 4787 16 0  
## 4875 4875 18 0  
## 4915 4915 16 0  
## 4928 4928 12 0  
## 4945 4945 11 0  
## 4977 4977 19 0  
## 5018 5018 12 0  
## 5112 5112 14 0  
## 5146 5146 14 0  
## 5184 5184 12 0  
## 5250 5250 15 0  
## 5336 5336 19 0  
## 5459 5459 14 0  
## 5546 5546 16 0  
## 5562 5562 17 0  
## 5583 5583 12 0  
## 5602 5602 16 0  
## 5619 5619 15 0  
## 5695 5695 11 0  
## 5743 5743 16 0  
## 5766 5766 14 0  
## 5851 5851 18 0  
## 5956 5956 17 0  
## 6087 6087 15 0  
## 6103 6103 12 0  
## 6150 6150 13 0  
## 6156 6156 11 0  
## 6225 6225 11 0  
## 6291 6291 20 0  
## 6295 6295 14 0  
## 6297 6297 16 0  
## 6323 6323 18 0  
## 6458 6458 15 0  
## 6567 6567 15 0  
## 6622 6622 11 0  
## 6683 6683 16 0  
## 6761 6761 15 0  
## 6764 6764 11 0  
## 6838 6838 16 0  
## 6900 6900 17 0  
## 6964 6964 19 0  
## 7035 7035 16 0  
## 7073 7073 13 0  
## 7117 7117 11 0  
## 7182 7182 12 0  
## 7282 7282 14 0  
## 7298 7298 16 0  
## 7329 7329 13 0  
## 7332 7332 17 0  
## 7345 7345 20 0  
## 7384 7384 11 0  
## 7616 7616 14 0  
## 7705 7705 20 0  
## 7718 7718 14 0  
## 7787 7787 18 0  
## 7811 7811 13 0  
## 7819 7819 11 0  
## 7834 7834 12 0  
## 7881 7881 14 0  
## 7971 7971 20 0  
## 8038 8038 17 0  
## 8092 8092 20 0  
## 8108 8108 11 0  
## 8268 8268 17 0  
## 8376 8376 11 0  
## 8382 8382 14 0  
## 8621 8621 16 0  
## 8660 8660 16 0  
## 8683 8683 18 0  
## 8731 8731 12 0  
## 8819 8819 16 0  
## 8890 8890 11 0  
## 8998 8998 15 0  
## 9023 9023 14 0  
## 9040 9040 20 0  
## 9071 9071 14 0  
## 9084 9084 17 0  
## 9172 9172 12 0  
## 9180 9180 11 0  
## 9264 9264 14 0  
## 9311 9311 16 0  
## 9321 9321 16 0  
## 9406 9406 13 0  
## 9469 9469 16 0  
## 9523 9523 11 0  
## 9541 9541 12 0  
## 9553 9553 15 0  
## 9556 9556 13 0  
## 9614 9614 12 0  
## 9624 9624 19 0  
## 9661 9661 11 0  
## 9689 9689 11 0  
## 9783 9783 13 0  
## 9787 9787 18 0  
## 9790 9790 16 0  
## 9847 9847 17 0  
## 9863 9863 19 0  
## 9923 9923 13 0  
## 10003 10003 20 0  
## 10060 10060 16 0  
## 10108 10108 17 0  
## 10180 10180 12 0  
## 10186 10186 14 0  
## 10193 10193 13 0  
## 10364 10364 16 0  
## 10398 10398 20 0  
## 10453 10453 13 0  
## 10469 10469 20 0  
## 10509 10509 14 0  
## 10660 10660 16 0  
## 10771 10771 14 0  
## 10964 10964 16 0  
## 10971 10971 11 0  
## 11023 11023 12 0  
## 11030 11030 11 0  
## 11034 11034 17 0  
## 11090 11090 19 0  
## 11151 11151 20 0  
## 11154 11154 15 0  
## 11196 11196 16 0  
## 11288 11288 17 0  
## 11296 11296 13 0  
## 11306 11306 17 0  
## 11328 11328 17 0  
## 11397 11397 11 0  
## 11447 11447 17 0  
## 11483 11483 17 0  
## 11526 11526 20 0  
## 11590 11590 14 0  
## 11644 11644 11 0  
## 11655 11655 14 0  
## 11670 11670 14 0  
## 11733 11733 19 0  
## 11793 11793 16 0  
## 11799 11799 13 0  
## 11846 11846 20 0  
## 11885 11885 11 0  
## 11886 11886 18 0  
## 11896 11896 17 0  
## 11988 11988 16 0  
## 12234 12234 19 0  
## 12290 12290 12 0  
## 12309 12309 15 0  
## 12361 12361 18 0  
## 12385 12385 13 0  
## 12561 12561 11 0  
## 12583 12583 11 0  
## 12604 12604 18 0  
## 12612 12612 11 0  
## 12727 12727 12 0  
## 12855 12855 13 0  
## 12861 12861 11 0  
## 13104 13104 11 0  
## 13120 13120 16 0  
## 13123 13123 17 0  
## 13138 13138 13 0  
## 13141 13141 11 0  
## 13146 13146 20 0  
## 13170 13170 15 0  
## 13177 13177 15 0  
## 13190 13190 17 0  
## 13259 13259 14 0  
## 13286 13286 17 0  
## 13347 13347 11 0  
## 13359 13359 15 0  
## 13392 13392 12 0  
## 13574 13574 12 0  
## 13601 13601 12 0  
## 13630 13630 18 0  
## 13671 13671 11 0  
## 13732 13732 14 0  
## 13736 13736 14 0  
## 13791 13791 13 0  
## 13895 13895 11 0  
## 13912 13912 12 0  
## 13926 13926 13 0  
## 13944 13944 18 0  
## 14090 14090 17 0  
## 14173 14173 11 0  
## 14174 14174 17 0  
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The output from *Pruning\_info* includes the variants to prune, notated by what line they are in the haplotype file, the current allele count, and the new minor allele count. Variants that will either have all or a subset of minor alleles removed.

#### 2) Pruning Implementation

There is (or soon will be) an example on the [RAREsim github page](https://github.com/meganmichelle/RAREsim/blob/master/HAPGEN2_simulation_example) that shows how to implement the pruning.

Pruning requires the haplotype and legend files that are being pruned and the output from the *Pruning\_info* function.