**Title:** On the reconciliation for SNP-based Heritability and genomic heritability using Haseman-Elston regression

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**Abstract**

SNP-based heritability that quantifies the phenotypic variation captured by genome-wide single nucleotide polymorphism (SNP) markers is a device towards the understanding of complex traits. Given many empirical results published in recent years, the exact structure of SNP-based heritability remains a state of obscurity. In this study, using a modified Haseman-Elston regression (HE), a model-free method that promises analytical results, we have established the formal genetic interpretation of SNP-based heritability by crystalizing its mathematical structure, for both additive and dominance genetic components, respectively. The analytical results were shorthanded by matrix algebra and easy for further extension. Simulation examples and real data examples using UK Biobank and 1KG data is demonstrated.

**Keywords**: complex traits, SNP-based heritability, genomic-heritability, Haseman-Elston regression, genetic relationship matrix.

# Introduction

As a parameter of broad interest and utility, heritability () is a device towards various genetic applications, such as for the inference of “missing heritability” and genetic architecture (Manolio *et al.* 2009; Yang *et al.* 2010). Using single nucleotide polymorphism (SNP) to estimate SNP-heritability , for example, comparison has been implemented to evaluate via realized quantity of under different SNP markers (Yang *et al.* 2015) and different methods (Speed *et al.* 2017). Endeavours have been casted to crystalize under the context of the maximum likelihood framework (Lee and Chow 2014; de los Campos *et al.* 2015; Legarra 2016; Steinsaltz *et al.* 2018); due to the obscure nature of restricted maximum likelihood (REML), even though after nearly a decade search by employing larger and larger sample size, the interpretation or comparison of the suggested estimates of remains empirical (Yang *et al.* 2017).

Besides REML, there is alternative route for the estimation of : the least-squares estimation, known as Hasemen-Elston regression (HE)—which seems less nourished. The original HE is identity by descent (IBD) for linkage analysis (Haseman and Elston 1972), but has recently been modified for association analysis after its IBD was replaced by identical by state (IBS) (Chen 2014). In two perspectives the HE route should be investigated or further clarified. In terms of computational complex in the estimation of , REML is approximately cubic of the sample size [] but HE the square of the sample size [], an computational advances that is in need for biobank-scale data (Bycroft *et al.* 2018; Liu *et al.* 2018), recent studies are focused on the modified HE and its feasible applications in estimating variance component for (Ge *et al.* 2017; Ott *et al.* 2017; Sofer 2017).

Among many possible approaches to estimating . The central question is what the exact structure of them. In this work, we crystalize the mathematical structure of via HE, which promises analytical results for the structure of the SNP-heritability. In addition to the additive variance component (), we provide the analytical result for SNP-heritability for dominance variance component (). We provide the analytical results for both additive and dominance under the weighted schemes of the genetic relationship matrices (VanRaden 2008; Goudet *et al.* 2018); the weighted form of SNP-heritability is often referred as “genomic heritability” (de los Campos *et al.* 2015).

From an alternative perspective, the goal of the study can be understood as below. Of a trait its real heritability is the “inner mass”, but is perceived “mass” upon the instrument (such as SNPs) and the method (such as HE). In addition, “inner mass” is define regardless how heritability is measured in practice. In this analysis, we will explore the relationship between the “inner mass” – the reference heritability and the “measured mass”— SNP-heritability.

# Materials and Methods

**Data description**

## Haseman-Elston regression

The seminal HE regresses the squared phenotypic difference to IBD scores for a pair of siblings; via least squares approach, the estimated HE regression coefficient has an elegant analytical result (Haseman and Elston 1972). In this study, we replace the pair of the conventional relatives to unrelated individuals (in term of its conventional meaning), and the modified linear regression is as below

(**Eq 1**)

is the squared-difference for a pair of unrelated samples and ; given samples, is a vector of elements. can be constructed as additive genetic relatedness or dominance genetic relatedness, respectively. Furthermore, weights can be introduced for (VanRaden 2008). So, in total four possible forms of are considered here: additive relatedness, dominance relatedness, additive relatedness with weights, and dominance relatedness with weights.

## Additive genetic relatedness

For a single locus, orthogonal coding scheme separates the genetic variance into additive and dominance genetic variances (Vitezica *et al.* 2017). Under the assumption of Hardy-Weinberg equilibrium (HWE), for the individual, the additive and the dominance code schemes for the locus are and for , respectively. The allele frequency of the locus is . Under HWE, the genotypic frequencies of , , and are , , and , respectively. After standardization, we have , a vector of elements (SNPs); for dominance genetic relatedness, we have .

A genetic relationship matrix, of dimension , can be constructed in terms of the additive effects; between individuals and , their SNP-based additive genetic relatedness can be written as

(**Eq 2**)

in which is a diagonal matrix, via which weights can be introduced, and and is the trace of .

When there are no weights introduced for the relatedness, an identity matrix, . It is often used in human genetics for the estimation of , denoted as thereafter. When the weight is introduced, for example and . In parallel to the unweighted form, the weighted form of SNP-based heritability, denoted as thereafter, leads to genomic heritability (de los Campos *et al.* 2015).

Let denote the off-diagonal elements of . Itis easy to see that

**(Eq 3)**

, and we further denote

**(Eq 4)**

a quantity indicating the effective number of markers. Or, when has been weighted, .

## Dominance relatedness

Similarly, we can define the genetic relatedness in terms of dominance effects

(**Eq 6**)

in which is a diagonal matrix. When there is no weight introduced, , and ; when weight is introduced, .

Similarly, we can define

**(Eq 7)**

and

**(Eq 8)**

In contrast, when is weighted, .

## The structure of for additive variance component

In deriving the structure of , and a stochastic modeling method that uses conditional probability has been presented in Chen (2014). The key step is to find the elements for additive SNP-heritability, . For a biallelic locus, there are nine possible combinations, but merged to six combinations, for and , respectively, as found in Table 1. The technical details in defining each element please refer to Chen (2014). Compared with Chen’s work in 2014, we introduce the term of weight, for additive variance component, ; in contrast, when , it becomes the SNP-heritability as original derived in Chen (2014)

Upon is fitted in Eq 1, the derived SNP-based heritability is (Eq 5)

this expression is equivalent to Eq 10 in Chen’s original paper (Chen 2014). It is important to notice that is an aggregated relatedness, and as promised by HE we can elucidate how each marker, such as the SNP, tag the causal variants. The numerator can be rearranged to have the form as below

Of note, the matrix, , represents how the causal variants are connected to each other but via the SNP. As a comparison, if this matrix is replaced with , the hidden correlation matrix between any pair of causal variants, and the real heritability can be defined correspondingly,

We can shorthand SNP-based heritability in matrix form as below

**(Eq 6)**

in which is the vector for additive effects, an matrix, as demonstrated above, that describes the correlation between causal variants but via the marker, is a diagonal matrix with element , is a matrix that . is the vector of 1.

The standard error of the estimated SNP-heritability is

We look inside and analyze its response to genetic architecture, we can partition the into the diagonal part and the off-diagonal part ,

Under the infinitesimal model, can be dropped off, and . It is because the terms are associated with the covariance terms that will trade off each other under the infinitesimal model. Of note, , the classic definition of , resembles Eq 7. the correlation matrix between causal variants. Eq 8 only holds when , it is equivalent to set the correlation matrix between causal variants. However, when causal variants are randomly distributed, is reduced to the identity matrix.

However, it does not mean can be ignored universally. We will present example, albeit pathological though, at a very two-locus scenario (see example below). Only when is turned off, the linear connection between SNP-based heritability and heritability is possible, and consequently for the task of the estimation and inference of missing heritability.

When the causal variants are randomly distributed along the genome, .

**(Eq 8)**

in which , the averaged LD between a SNP and a causal variantand , the averaged LD between a pair of SNPs.

As a comparison, “genomic-heritability” is emphasized by de los Campos et al (2015), in which is introduced as weight for the genetic relatedness. Using similar stochastic modeling approach, the regression coefficient in HE is

We can find how the marker tags the causal variants as below

If we take as weight to , the genomic-heritability, denoted as herein, has its mathematical structure

(Eq 7)

Obviously, will be have set to 1 – no weights consequently. The standard error of the estimated genomic heritability is

## SNP-based heritability for dominance variance

If is constructed for dominance effect and fitted into Eq 1, it is to find the elements, in Table X, for

in which is the vector for the dominance effects, , and indicating the LD between the marker and the causal variant regarding the dominance effects. Similar to “genomic heritability”, we can introduce to , the regression coefficient is

So, upon the analysis above four SNP-heritability/genomic-heritability can be derived.

Furthermore, for a pair of traits, their corresponding SNP-based coheritability can be derived correspondingly, summarized in Table X. Compared with SNP-heritability, for example , that has symmetric mathematic form, the co-heritability in contrast,

has an asymmetric form because of and causal variants underlying the pair of traits. has the length of , a diagonal matrix of elements, and , is an matrix.

The classic definition of narrow-sense heritability can be expressed in matrix (Lynch and Walsh 1998),

**(Eq 9)**

in which a symmetric square matrix that its element characterizing the LD structure between any pair of causal loci.

## Genetic architecture

For a pair of traits, if there are randomly causal loci are shared and have a correlation of between two traits, then we have

in which , and in particular is the averaged squared LD between the tag SNPs are the shared causal loci, but not all causal loci as for the single trait.

**Genetic architecture**

The difference between and is that of in Eq 9 and in Eq 5, and between and is that of and . Under NGA that all causal variants are randomly distributed along the genome and their effects follow a normal distribution , in particular, the effect size is independent of allele frequency or LD, both and can be simplified:

**(Eq 9)**

and

**(Eq 10)**

in which is the averaged squared LD between the SNP markers and the causal variants and the averaged squared LD between SNPs. Equation 9 is used as a device in linear mixed model system; equation 10 is probably the most often used device in the inference of genetic architecture (Yang *et al.* 2017).

Of note, under the NGA, the weighted and unweighted version of SNP-heritability were equivalent.

Alternatively, if not more ubiquitously, causal variants are not randomly distributed along the genome. Under SGA, the analytical result of is as Eq 3, with weight, or Eq 4, without weight has no linear transform between towards . We demonstrate that under NGA, with and without weights are theoretically identical, and consequently should not be statistically different. The difference between Eq 3 and Eq 4 is the crux of NGA and NNGA.

# Results

**Numerical example for the connection between the estimated heritability and the inner heritability**

Consider a special case that of two equal-frequent QTLs, both of which are genotyped. Their effect size are both 1, and the LD between them is . The heritability can be written as

and .

After rearrangement, . Although it is a very special case, it indicates that “inner” heritability and the estimated SNP-heritability is not necessary equal. O note, for this case, as the allele frequency is the same, introducing weight will not differ and .

“/Users/gc5k/manuscript/Linkage\_Association/submit/FrontGenet/2qtl”

## Numerical examples for SNP-based heritability

**The data on cluster linfeng/ukb/British/NGA\_test**

**5000 sample, 2 loci, random maf, dprime -1 to 1.**

Given the analytical results, we first validated their accuracy in simulation studies. We simulated a pair of loci, both of which had their allele frequency randomly distributed, and they were in LD, which was capped by their allele frequencies. The genetic effects were also simulated randomly. The heritability, “inner mass”, was set to 0.5. Similarly, we also tested dominance model. The simulation results were consistent with our **Eq 3-6** as derived above (data not shown; /public/home/xuhm/linfeng/ukb/EqSimu/NGA\_NNGA & /public/home/xuhm/linfeng/ukb/EqSimu/NGA\_NNGA\_dom).

Given the analytical results above, we compared and evaluated the discrepancy between the real heritability, the “inner mass”, and the SNP-based heritability, the “measured mass”. To have manual example, we only consider a pair of casual variants only. In order to give a clear picture how SNP-based heritability worked. We provided a very simple numerical example for a pair of loci. The allele frequencies for these two loci were and , respectively, and the additive effect were and , respectively. The squared correlation between them was , and the maximum of was 0.577. We have the realized matrices below

, , , , and ; for the weighted SNP-based heritability, , , whereas the unweighted , and . Given and , the range for is -0.577 to 0.577.

We gave a manual example for ,

we had “inner mass” , the “measured mass” without weight is

and the weighted one is

The full range of the result was show in Figure X below.

This above example shown the discrepancy among three kinds of heritability because the genetic effects were negative associated with allele frequency, simulating signature of selection. In contrast, we simulated another example, in which and , so the genetic effect is not associated to the allele frequency. Under this example, when three estimates had the same value (Figure X /public/home/xuhm/linfeng/ukb/EqSimu/heProperties).

One conclusion from this simple simulation was that the estimated SNP-heritability could be smaller, in particular even larger, than the real heritability. However, this discrepancy will disappear when the trait is controlled by many loci.

## UK Biobank analysis

# Discussion

The purpose of the study is to derive the connection between heritability and SNP-heritability, and to clarify the circumstance that SNP-heritability can be approximated by heritability under the neutral genetic architecture. Using modified HE and based on our results established previously (Chen 2014, 2016), we derived the mathematical expression of SNP-heritability for both additive and dominance terms. However, due to materials used – high density SNP markers and the method used – numerator relationship matrix, SNP-heritability differ from heritability by the way LD are represented. In its classic definition, heritability is perfectly measured on QTLs directly, but in estimation the LD to the casual variants is tagged via markers.

In addition, we introduced the matrix algebra that can shorthand the structure of SNP-heritability succinctly. Given the crystallization of SNP-heritability, it also paves the road to construct effective hypotheses test for genetic architecture ***in silicon***. The general idea in testing varying genetic architecture is to introduce proper weights, a commonly adopted technique in linear algebra. Although we only demonstrated one kind of weights, obviously a family of weights can be introduced systematically according to the genetic architecture of interest. It relies on the further work for refined exploration of genetic architecture and real data will be tested in the future.

For UK Biobank data, within either UK-CH or UKW the weighted and unweighted forms SNP-heritability similar to each other for 65 quantitative traits analyzed. However, the difference between them were more visible. So, in general, we conclude at the whole-genome scale, the dependency between allele frequency and casual effects should be marginal.

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# Literature cited

Altshuler D. M., Gibbs R. A., Peltonen L., Dermitzakis E., Schaffner S. F., Yu F., Bonnen P. E., Bakker P. I. W. de, Deloukas P., Gabriel S. B., Gwilliam R., Hunt S., Inouye M., Jia X., Palotie A., Parkin M., Whittaker P., Chang K., Hawes A., Lewis L. R., Ren Y., Wheeler D., Muzny D. M., Barnes C., Darvishi K., Hurles M., Korn J. M., Kristiansson K., Lee C., McCarrol S. A., Nemesh J., Keinan A., Montgomery S. B., Pollack S., Price A. L., Soranzo N., Gonzaga-Jauregui C., Anttila V., Brodeur W., Daly M. J., Leslie S., McVean G., Moutsianas L., Nguyen H., Zhang Q., Ghori M. J. R., McGinnis R., McLaren W., Takeuchi F., Grossman S. R., Shlyakhter I., Hostetter E. B., Sabeti P. C., Adebamowo C. A., Foster M. W., Gordon D. R., Licinio J., Manca M. C., Marshall P. A., Matsuda I., Ngare D., Wang V. O., Reddy D., Rotimi C. N., Royal C. D., Sharp R. R., Zeng C., Brooks L. D., McEwen J. E., 2010 Integrating common and rare genetic variation in diverse human populations. Nature **467**: 52–8.

Bycroft C., Freeman C., Petkova D., Band G., Elliott L. T., Sharp K., Motyer A., Vukcevic D., Delaneau O., O’Connell J., Cortes A., Welsh S., Young A., Effingham M., McVean G., Leslie S., Allen N., Donnelly P., Marchini J., 2018 The UK Biobank resource with deep phenotyping and genomic data. Nature **562**: 203–209.

Chen G.-B., 2014 Estimating heritability of complex traits from genome-wide association studies using IBS-based Haseman-Elston regression. Front. Genet. **5**: 107.

Chen G.-B., 2016 On the reconciliation of missing heritability for genome-wide association studies. Eur. J. Hum. Genet. **24**: 1810–6.

Ge T., Chen C.-Y., Neale B. M., Sabuncu M. R., Smoller J. W., 2017 Phenome-wide heritability analysis of the UK Biobank. PLoS Genet. **13**: e1006711.

Goudet J., Kay T., Weir B. S., 2018 How to estimate kinship. Mol. Ecol. **27**: 4121–4135.

Haseman J. K., Elston R. C., 1972 The investigation of linkage between a quantitative trait and a marker locus. Behav. Genet. **2**: 3–19.

Lee J. J., Chow C. C., 2014 Conditions for the validity of SNP-based heritability estimation. Hum. Genet. **133**: 1011–22.

Legarra A., 2016 Comparing estimates of genetic variance across different relationship models. Theor. Popul. Biol. **107**: 26–30.

Liu S., Huang S., Chen F., Zhao L., Yuan Y., Francis S. S., Fang L., Li Z., Lin L., Liu R., Zhang Y., Xu H., Li S., Zhou Y., Davies R. W., Liu Q., Walters R. G., Lin K., Ju J., Korneliussen T., Yang M. A., Fu Q., Wang J., Zhou L., Krogh A., Zhang H., Wang W., Chen Z., Cai Z., Yin Y., Yang H., Mao M., Shendure J., Wang J., Albrechtsen A., Jin X., Nielsen R., Xu X., 2018 Genomic analyses from non-invasive prenatal testing reveal genetic associations, patterns of viral infections, and Chinese population history. Cell **175**: 347–359.

los Campos G. de, Sorensen D., Gianola D., 2015 Genomic heritability: what is it? PLoS Genet. **11**: e1005048.

Lynch M., Walsh B., 1998 *Genetics and Analysis of Quantitative Traits*. Sinauer Associates, Inc., Sunderland, MA, USA.

Manolio T. A., Collins F. S., Cox N. J., Goldstein D. B., Hindorff L. a, Hunter D. J., McCarthy M. I., Ramos E. M., Cardon L. R., Chakravarti A., Cho J. H., Guttmacher A. E., Kong A., Kruglyak L., Mardis E., Rotimi C. N., Slatkin M., Valle D., Whittemore A. S., Boehnke M., Clark A. G., Eichler E. E., Gibson G., Haines J. L., Mackay T. F. C., McCarroll S. a, Visscher P. M., 2009 Finding the missing heritability of complex diseases. Nature **461**: 747–53.

Ott A., Liu S., Schnable J. C., Yeh C. T. E., Wang K. S., Schnable P. S., 2017 tGBS® genotyping-by-sequencing enables reliable genotyping of heterozygous loci. Nucleic Acids Res. **45**: e178.

Sofer T., 2017 Confidence intervals for heritability via Haseman-Elston regression. Stat. Appl. Genet. Mol. Biol. **16**: 259–273.

Speed D., Cai N., Johnson M. R., Nejentsev S., Balding D. J., 2017 Reevaluation of SNP heritability in complex human traits. Nat. Genet. **49**: 986–992.

Steinsaltz D., Dahl A., Wachter K. W., 2018 Statistical properties of simple random-effects models for genetic heritability. Electron. J. Stat. **12**: 321–358.

VanRaden P. M., 2008 Efficient methods to compute genomic predictions. J. Dairy Sci. **91**: 4414–4423.

Vitezica Z. G., Legarra A., Toro M. A., Varona L., 2017 Orthogonal Estimates of Variances for Additive, Dominance and Epistatic Effects in Populations. Genetics **206**: 1297–1307.

Yang J., Benyamin B., McEvoy B. P., Gordon S., Henders A. K., Nyholt D. R., Madden P. A., Heath A. C., Martin N. G., Montgomery G. W., Goddard M. E., Visscher P. M., 2010 Common SNPs explain a large proportion of the heritability for human height. Nat. Genet. **42**: 565–569.

Yang J., Bakshi A., Zhu Z., Hemani G., Vinkhuyzen A. a E., Lee S. H., Robinson M. R., Perry J. R. B., Nolte I. M., Vliet-Ostaptchouk J. V van, Snieder H., Esko T., Milani L., Mägi R., Metspalu A., Hamsten A., Magnusson P. K. E., Pedersen N. L., Ingelsson E., Soranzo N., Keller M. C., Wray N. R., Goddard M. E., Visscher P. M., 2015 Genetic variance estimation with imputed variants finds negligible missing heritability for human height and body mass index. Nat. Genet. **47**: 1114–1120.

Yang J., Zeng J., Goddard M. E., Wray N. R., Visscher P. M., 2017 Concepts, estimation and interpretation of SNP- based heritability. Nat. Genet. **49**: 1304–10.

# Figure legends

**Figure 1 A minimal example for illustrating how SNP-heritability upon allele frequency and linkage disequilibrium.** The reference heritability is as defined in equation 9, and the estimates were scaled to have 0.5.



**Figure 2 SNP-heritability for 1436 UK Biobank Chinese (CH) and 1,000 UK whites (UKW) for 65 quantitative traits.** Only core SNPs that were minor allele frequencies greater than 0.01 in both CH and UK were used for the estimation. The first row: **Left**) SNP-heritability, without weight (x-axis) and with weight (y-axis), for UKBiobank Chinese over 65 quantitative traits; **Right**) estimated SNP-heritability for 1,000 UK Biobank whites for 65 quantitative traits. The second row: **Left**) Contrast for the SNP-heritability, without weight, for CH and UKW; **Right**) Contrast for SNP-heritability, with weight, for CH and UKW.



**Table 2** The joint distribution of the additive genetic relatedness between individual and

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|  | Individual | | | |  | Individual | | | | | |  | Relatedness for individual and | |
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**Notes:** and have subscript “A”, for additive, dropped off here.

As allele is set the reference allele, the frequency of which was , , , and were coded as 0, 1 and 2, respectively.

**Table 1** The joint distribution of the dominance genetic relatedness between individual and

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Individual | | | |  | Individual | | | | |  | Relatedness for individual and | |
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**Notes:** and have subscript “D”, for dominance, dropped off here.

**Table 1 Symbols for the structure of various SNP-based heritabilities**

|  |  |  |
| --- | --- | --- |
| **Symbol** | **Additive-related** | **Dominance-related** |
| Effect | is the vector of elements and . and are additive and dominance effects, respectively, of the locus. | is the vector of elements and its element is . |
| Allele frequency | a diagonal matrix, and . | a diagonal matrix, and . |
| Linkage disequilibrium | represents the linkage disequilibrium between the marker and each of the causal variants. | represents the squared correlation between the marker and each of the causal variants. |
| is an matrix, and . | is an matrix, and . |
| Weighting | , an vector. | , an vector. |
| a diagonal matrix, and . | a diagonal matrix, and . |
| Allele frequency | a diagonal matrix, and . | a diagonal matrix, and . |

Of note, ,, ,and are all hidden variables; the number of causal loci, the number of SNP loci.

**Table 2 The matrix presentation of SNP-heritability for additive and dominance genetic components**

|  |  |  |
| --- | --- | --- |
|  | **Additive** | **Dominance** |
| **Single traits** | | |
|  |  |  |
| No weight |  |  |
| Weighted |  |  |
| **A pair of traits** | | |
| No weight |  |  |
| Weighted |  |  |

**Table 3 Evaluation of and using HapMap populations without weight**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Population** |  |  |  |  |  |  |  |  |  |
| **Scenario I** |  |  |  |  |  |  |  |  |  |
| CHB (103) | -0.0098 | 103.36 |  | 907,614 | 2.16e-5 | 46,202.62 |  | 9.58e-6 | 104,345.31 |
| JPT (104) | -0.0097 | 104.27 |  | 2.95e-5 | 43,603.59 |  | 1.04e-5 | 96,411.15 |
|  |  |  |  |  |  |  |  |  |
| CEU (99) | -0.0102 | 99.37 |  | 2.58e-5 | 38,685.66 |  | 3.98e-5 | 106,740.08 |
| TSI (107) | -0.0094 | 107.31 |  | 2.35e-5 | 44,933.03 |  | 9.01e-6 | 110,963.01 |
|  |  |  |  |  |  |  |  |  |
| MSL (85) | -0.0118 | 85.46 |  | 4.22e-5 | 23,707.74 |  | 4.35e-6 | 229,848.07 |
| YRI (108) | -0.0093 | 108.43 |  | 1.21e-5 | 82,638.06 |  | 4.44e-6 | 225,221.38 |
| **Scenario II** (MAF > 0.05) | | | | |  |  |  |  |  |
| CHB (103) | -0.0098 | 103.36 |  | 824,710 | 2.47e-5 | 40,520.49 |  | 1.13e-5 | 80,725.48 |
| JPT (104) | -0.0097 | 104.27 |  | 820,982 | 2.61e-5 | 38,244.57 |  | 1.23e-5 | 80,997.89 |
|  |  |  |  |  |  |  |  |  |  |
| CEU (99) | -0.0102 | 99.37 |  | 851,342 | 2.79e-5 | 35,841.94 |  | 1.04e-5 | 96,601.30 |
| TSI (107) | -0.0094 | 107.31 |  | 852,354 | 2.42e-5 | 41,277.66 |  | 1.00e-5 | 99,675.29 |
|  |  |  |  |  |  |  |  |  |  |
| MSL (85) | -0.0118 | 85.46 |  | 816,393 | 4.58e-5 | 21,817.77 |  | 5.20e-6 | 192,279.34 |
| YRI (108) | -0.0093 | 108.43 |  | 819,671 | 1.37e-5 | 72,781.09 |  | 5.27e-6 | 189,590.34 |

**Table 4 Evaluation of and using 1KG samples with weights**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Population** | |  |  | |  |  |  |  |  |  |  |
| **Scenario I** | |  |  | |  |  |  |  |  |  |  |
| CHB (103) | | -0.0098 | 103.36 | |  | 907,614 | 2.81e-5 | 35,552.12 |  | 1.64e-5 | 61,095.14 |
| JPT (104) | | -0.0097 | 104.28 | |  | 2.92e-5 | 34,231.47 |  | 1.77e-5 | 56,463.71 |
|  | |  |  | |  |  |  |  |  |  |
| CEU (99) | | -0.0102 | 99.39 | |  | 3.12e-5 | 32,043.18 |  | 1.47e-5 | 67,815.78 |
| TSI (107) | | -0.0094 | 107.33 | |  | 2.75e-5 | 36,318.51 |  | 1.43e-5 | 70,057.59 |
|  | |  |  | |  |  |  |  |  |  |
| MSL (85) | | -0.0118 | 85.47 | |  | 4.75e-5 | 21,066.03 |  | 7.47e-6 | 133,810.81 |
| YRI (108) | | -0.0093 | 108.43 | |  | 1.54e-5 | 65,115.82 |  | 7.75e-6 | 129,057.08 |
| **Scenario II** (MAF > 0.05) | | | | | | |  |  |  |  |  |
| CHB (103) | -0.0098 | | 103.36 |  | | 824,710 | 2.89e-5 | 34,655.78 |  | 1.64e-5 | 60,805.68 |
| JPT (104) | -0.0097 | | 104.28 |  | | 820,982 | 2.99e-5 | 33,411.80 |  | 1.78e-5 | 56,193.86 |
|  |  | |  |  | |  |  |  |  |  |  |
| CEU (99) | -0.0102 | | 99.37 |  | | 851,342 | 3.16e-5 | 31,635.78 |  | 1.48e-5 | 67,628.51 |
| TSI (107) | -0.0094 | | 107.32 |  | | 852,354 | 2.79e-5 | 35,782.68 |  | 1.43e-5 | 69,852.85 |
|  |  | |  |  | |  |  |  |  |  |  |
| MSL (85) | -0.0118 | | 85.47 |  | | 816,393 | 4.81e-5 | 20,811.19 |  | 7.51e-6 | 133,189.46 |
| YRI (108) | -0.0093 | | 108.44 |  | | 819,671 | 1.57e-5 | 63,781.53 |  | 7.78e-6 | 128,491.57 |

**Notes**: CHB, Chinese in Beijing; JPT, Japanese in Tokyo; MSL, Mende in Sierra Leone; YRI, Yoruba in Ibadan, Nigeria; CEU, Utah residents with Northern and Western European ancestry; TSI, Tuscani in Italy.

**1KG samples**

We examined the and using HapMap data (Altshuler *et al.* 2010) in three major ethnicities: Asians (103 Chinese in Beijing, CHB; 104 Japanese in Tokyo, JPT), Europeans (99, Utah residents with Northern and Western European ancestry, CEU; 107 Tuscani in Italy, TSI), and Africans (85 Mende in Sierra Leone, MSL; 108 Yoruba in Ibadan Nigeria, YRI).

When using 907,614 SNP markers that had MAF greater than 0.05 for these HapMap cohorts, was always very close the sample size for each of the six cohorts (**Table 3**). In contrast, the variance of GRM varied across the populations reflecting the different LD structure underlying each cohort.

We only used the alleles having minor allele frequency (MAF) greater than 0.05 in each cohort. The estimated was always very close the actual sample size for each of the six cohorts, indicating that each sample was randomly collected. was of little change. Interestingly, for its largest and smallest numbers were observed in MSL (82,638.06) and YRI (23,707.74), both African populations; while Asian and European population had relative median values about from 38,685.66 in to 46,202.62 in CHB. For , the pattern was similar, but both African cohorts showed largest values, about 225K~229K, while nearly halved in that of the other two ethnicities (**Table 3**). When was weighted by and was weighted by , the results resembled the one that without weight (**Table 4**).

**Table 4 1000 samples for SNP markers with MAF > 0.01 in all three populations**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Sample size | Marker |  |  | **(weighted)** |  |  | **(weighted)** |
| 1,000 Africans | 324,012 |  | 1,925.44 | 35,82.87 |  | 27,486.49 | 74,809.44 |
| 1,000 Chinese | 324,012 |  | 18,665.02 | 20,286.95 |  | 79,020.11 | 53,832.35 |
| 1,000 UK | 324,012 |  | 43,220.85 | 32,412.13 |  | 114,417.03 | 60,919.29 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Center | Marker |  | (weighted) |  | **(weighted)** |
| Manchester | 476499 | 1.81E-05 | 2.75E-05 | 55127.40 | 36343.28 |
| Oxford | 476499 | 1.76E-05 | 2.69E-05 | 56737.27 | 37126.14 |
| Cardiff | 476336 | 1.87E-05 | 2.84E-05 | 53452.78 | 35196.40 |
| Glasgow | 476558 | 1.88E-05 | 2.88E-05 | 53260.90 | 34697.64 |
| Edinburgh | 476486 | 1.84E-05 | 2.81E-05 | 54430.95 | 35595.42 |
| Stoke | 476708 | 1.90E-05 | 2.82E-05 | 52681.77 | 35479.49 |
| Reading | 476297 | 1.67E-05 | 2.59E-05 | 59735.02 | 38584.27 |
| Bury | 476672 | 1.77E-05 | 2.70E-05 | 56631.88 | 36996.07 |
| Newcastle | 476670 | 1.78E-05 | 2.72E-05 | 56210.72 | 36789.19 |
| Leeds | 476620 | 1.72E-05 | 2.64E-05 | 58116.22 | 37831.07 |
| Bristol | 476454 | 1.71E-05 | 2.63E-05 | 58423.16 | 37969.25 |
| Barts | 476010 | 1.88E-05 | 2.76E-05 | 53107.31 | 36200.93 |
| Nottingham | 476440 | 1.73E-05 | 2.65E-05 | 57740.05 | 37673.44 |
| Sheffield | 476740 | 1.76E-05 | 2.69E-05 | 56811.73 | 37122.83 |
| Middlesborough | 476575 | 1.82E-05 | 2.76E-05 | 54883.24 | 36296.19 |
| Hounslow | 476166 | 1.71E-05 | 2.63E-05 | 58394.84 | 38062.47 |
| Croydon | 476209 | 1.69E-05 | 2.61E-05 | 59041.98 | 38360.47 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Additive |  |  |  |  |
| UK1K | 0.602 |  |  |  |  |
|  | 0.4043 |  |  |  |  |
|  |  |  |  |  |  |
| CH1K | 1.605 |  | CHUK (1435) | 1.809 |  |
|  | 1.57 |  |  | 1.57 |  |
|  |  |  |  |  |  |
| AF1K | 0.2288 |  | AFUK (2819) | 0.7689 |  |
|  | 0.3337 |  |  | 0.7507 |  |

CH1K and AF1K only used SNPs passed QC of MAF > 0.01 in three ethnicities, and in total 324,012 SNPs are found.

CHUK: using projected PC with 1kg as the reference to find Chinese and using 324012 SNPs above.

AFUK: using projected PC with 1KG as the reference to find African and using 324012 SNPs above.