Estimation of SNP Heritability from Dense Genotype Data

To the Editor: Recently, Speed et al.[1] undertook a comprehensive and elegant evaluation of five key assumptions underlying the linear mixed model implemented in the program GCTA[2] for estimation of SNP heritability.[3–6] They concluded that the method is robust to violations of four of the assumptions. However, they found that SNP-heritability estimates were sensitive to uneven linkage disequilibrium (LD) between SNPs (implying uneven tagging of causal variants) and suggested an approach to improving the robustness of estimates in this context. Speed et al.[1] tested their method on relatively sparse genotyping data (~300,000 SNPs) and showed that a weighted genomic-relationship matrix (GRM) performed better than the standard GRM when there was substantial unevenness in LD between SNPs in regions in which causal variants lie. They showed that biased estimates can result whenever the underlying genetic architecture of the traits differs from the genetic architecture assumed in the GRM definition (whether standard or weighted). However, it is unclear whether the method proposed by Speed et al.[1] will perform similarly on both dense and sparse genotyping data.

Here, we show that in the context of dense genotyping (e.g., imputation to the 1000 Genomes Project reference sample), the weighted GRM proposed by Speed et al.[1] might not be an optimal approach. We show that a minor allele frequency (MAF)-stratified approach gives SNP-heritability estimates that are robust to genotyping density and underlying genetic architecture of the traits. The MAF-stratified approach has been used for dissecting differences in genetic architecture by MAF.[7]

The linear mixed model for estimation of SNP heritability[8] fits the realized GRM estimated from whole-genome SNP data. The variance components are estimated by residual-maximum-likelihood analysis.[2,9] The realized relationship between individuals i and j can be estimated from L SNPs as

$$\widehat{A}_{ij} = \frac{1}{L}\sum_{l=1}^{L}\left(x_{l[i]} - 2p_l\right)\cdot\left(x_{l[j]} - 2p_l\right)\cdot \mathrm{var}(x_l)^s, \quad \text{(Equation 1)}$$

where $x_{l[i]}$ represents the genotype of individual i at locus l ($x_l = 0$, 1, or 2 depending on the number of reference alleles), p is the allele frequency of the reference allele (and q is the frequency of the other allele, $q = 1 - p$), and $2p$ and $\mathrm{var}(x_l)$ are the mean and variance of x_l, respectively. The scale parameter s was introduced in Speed et al.[1] Most commonly, $s = -1$ (in Yang et al.,[8] Leutenegger et al.,[10] Amin et al.,[11] and VanRaden[12] and by default in GCTA) and scales by the heterozygosity for all SNPs across the genome,[8] but Speed et al. also considered varying s (e.g., $s = 0$, effect size independent of MAF).

Speed et al.[1] showed that if unbiased estimates of SNP heritability are to be achieved, the scale parameter s should be concordant with the variance of SNP allele effects—var(allele effect) $\propto [pq]^s$—i.e., that the underlying genetic architecture (which is unknown) is the same as the genetic architecture used in the construction of the GRM. They also noted that uneven tagging of causal variants by genotyped SNPs generated biased estimates of h^2_{SNP} under some genetic architectures. They proposed that SNP contributions should be weighted by the LD (r^2) between SNPs. However, we found that the weighted GRM can generate upwardly biased estimates of h^2_{SNP} in the context of dense genotyping because the density distribution of MAF, which is different from that in sparse genotyping, causes a suboptimal weighting strategy and thus attributes too much weight to the low-MAF SNPs. Here, we investigated an approach that breaks down the implicit relationship between SNP allele effects and heterozygozity by estimating h^2_{SNP} in a MAF-stratified approach that is more robust to a range of underlying genetic architectures, different MAF-density distributions, and hence unequal tagging of causal SNPs. We have previously[7] considered analyses in which SNP heritability is partitioned by MAF in order to provide insight into genetic architecture. In those analyses, a genomic relationship matrix was constructed from SNPs in MAF bin k via Equation 1 with $s = -1$. We used n = 5 for bins with MAF boundaries 0.1, 0.2, 0.3, 0.4, and 0.5. In this letter, we show that a robust estimate of h^2_{SNP} given a wide range of underlying genetic architectures is achieved from $h^2_{\mathrm{SNP}} = \sum_{k=1}^{n} V_{gk} / (\sum_{k=1}^{n} V_{gk} + V_e)$, where V_{gk} is the genetic variance of the k^{th} MAF bin and V_e is the residual variance.

Following Speed et al.,[1] we conducted simulations to check the robustness of the methods for estimating heritability on the basis of dense genotyping. We used genotype data[13] imputed to the reference panel. After quality control (imputation $R^2 > 0.6$, MAF > 0.01, cutoff $A_{ij} > 0.05$), there were 8,243,316 SNPs and 7,301 individuals. In each simulation replicate (50 replicates in total), 10,000 SNPs were assigned effects of normal distribution such that true $h^2 = 0.5$ for the simulated quantitative trait. In order to vary genetic architecture of the trait, we used var(allele effect) $\propto [p(1-p)]^s$ with $s = -1$ or 0. We also varied the genetic architecture by selecting the 10,000 causal SNPs at random (1) across the whole genome, (2) divided in the ratio 7:3 for MAF < 0.1 and MAF > 0.1, or (3) restricted to MAF < 0.1. Table 1 shows the proportion of causal SNPs and the true genetic variances across MAF bins for the six simulation strategies (architectures A–F). When $s = 0$, more variance is attributed to the higher MAF SNPs, i.e.,

Table 1. Simulation Strategies for Generating Different Genetic Architectures: A–F

	MAF					
	<0.1	0.1–0.2	0.2–0.3	0.3–0.4	0.4–0.5	Total
SNPs Selected at Random						
% causal SNPs	39	20	15	13	13	100
% variance attributable to causal SNPs for A: var(allele effect size) ~ $[p_iq_i]^{-1}$	19	10	8	7	6	50
% variance attributable to causal SNPs for B: var(allele effect size) ~ $[p_iq_i]^0$	6	9	11	12	12	50
SNPs Selected at Random but Distributed 7:3 for MAF < 0.1: MAF > 0.1						
% causal SNPs	70	10	7	7	6	100
% variance attributable to causal SNPs for C: var(allele effect size) ~ $[p_iq_i]^{-1}$	35	5	4	3	3	50
% variance attributable to causal SNPs for D: var(allele effect size) ~ $[p_iq_i]^0$	17	7	8	9	9	50
SNPs Selected at Random but Distributed for MAF < 0.1						
% causal SNPs	100	0	0	0	0	100
% variance attributable to causal SNPs for E: var(allele effect size) ~ $[p_iq_i]^{-1}$	50	0	0	0	0	50
% variance attributable to causal SNPs for F: var(allele effect size) ~ $[p_iq_i]^0$	50	0	0	0	0	50

effect sizes of the causal variants are independent from their MAFs so that common variants explain much more variance than do rare variants. When $s = -1$, more variance is attributed to lower-MAF SNPs, i.e., on average the variance explained by a common SNP and a rare SNP is equal (effect sizes for rare variants are larger), but there is a greater proportion of rarer SNPs. For each replicate, we estimated h^2_{SNP} on the basis of the standard GRM ($s = -1$), an alternate GRM ($s = 0$), the Speed et al. weighted GRM, and the MAF-stratified approach. For the weighted GRM, we obtained weighting scores for the SNPs by using the LDAK software.[1] We measured goodness of fit by the difference in the Akaike information criterion (ΔAIC) between the null model (without the genetic component) and the full model such that higher ΔAIC indicated better fit. The AIC is defined as AIC = $2v - 2\ln(\text{likelihood})$, where v is the number of variance components.

Unbiased estimates of h^2_{SNP} were achieved when the scaling factor used for calculating the GRM matched the scaling factor used for simulating effects sizes for both $s = 0$ and $s = -1$ (Table 2). However, the GRM based on $s = 0$ generated downwardly biased estimates of h^2_{SNP} when causal effects were generated under a model with $s = -1$ and the GRM based on $s = -1$ generated upwardly biased estimates of h^2_{SNP} when causal effects were generated under a model with $s = 0$ because of the relative emphasis placed on the sharing of variants of different MAFs. Moreover, we found that the Speed et al. weighted GRM gave upwardly biased estimates under both simulation architectures, a result not observed in their own simulations because they used a relatively sparse set of ~300,000 genotypes. We replicated their results when only ~300,000 genotypes were used (data not shown). As genotyping density increased, the percentage of SNPs with low MAF increased (and the proportion based on the effective number of independent SNPs was higher still; Table S1, available online). We compared estimates of SNP heritability when causal SNPs were excluded from construction of the GRM and showed that exclusion of causal SNPs generates underestimates of SNP heritability in the context of sparse genome-wide genotypes, but not dense genotyping (Table S2).

When a higher proportion of causal SNPs had low MAF (architectures C and D), the standard GRM gave biased estimates with either $s = -1$ or 0, confirming the results in Speed et al.[1] However, the estimate from the weighted GRM method was also biased. In contrast, the MAF-stratified approach gave values near the true values under all genetic architectures (Table 1). Only when all causal variants had MAF < 0.1 and effect sizes were independent of frequency (architecture F) did the MAF-stratified (as well as other) methods generate biased results; we were able to remedy this by fitting an additional MAF bin in the lowest frequency class (i.e., MAF < 0.05, 0.05 < MAF < 0.1) (Table S3). The estimates for each MAF bin in the MAF-stratified approach showed excellent agreement with the true simulated values in Table 1 (Table S4).

A higher ΔAIC implies a better fit of the analysis model to the data, and when causal SNPs were equally distributed across different MAFs, the highest ΔAIC was achieved for the GRM calculated from the equation that

Table 2. Comparisons of GRM Methods when the Genetic Architecture of the Simulated Trait Varies and the True Simulated h^2 Is 0.5

	Var(Allele Effect Size) ~ $[p_iq_i]^{-1}$		Var(Allele Effect Size) ~ $[p_iq_i]^0$	
	h^2_{SNP} (SD)	ΔAIC[a] (SD)	h^2_{SNP} (SD)	ΔAIC[a] (SD)
Causal Variants Randomly Assigned				
	Architecture[b] A		**Architecture[b] B**	
Standard GRM with $s = -1$	0.51 (0.04)	117 (20)	0.57 (0.04)	149 (24)
Standard GRM with $s = 0$	0.39 (0.04)	102 (19)	0.49 (0.03)	168 (24)
Speed et al. weighted GRM	0.56 (0.12)	31 (13)	0.59 (0.09)	35 (11)
MAF-stratified approach	0.51 (0.04)	113 (20)	0.51 (0.05)	164 (24)
Causal Variants Randomly Assigned in 7:3 Ratio for MAF < 0.1: MAF > 0.1				
	Architecture[b] C		**Architecture[b] D**	
Standard GRM with $s = -1$	0.45 (0.05)	93 (23)	0.53 (0.05)	128 (26)
Standard GRM with $s = 0$	0.29 (0.04)	58 (21)	0.42 (0.04)	123 (25)
Speed et al. weighted GRM	0.55 (0.10)	33 (18)	0.57 (0.10)	32 (11)
MAF-stratified approach	0.51 (0.05)	104 (19)	0.51 (0.05)	126 (26)
Causal Variants Randomly Assigned to MAF < 0.1				
	Architecture[b] E		**Architecture[b] F**	
Standard GRM with $s = -1$	0.38 (0.05)	65 (19)	0.44 (0.04)	86 (18)
Standard GRM with $s = 0$	0.18 (0.05)	21 (11)	0.23 (0.04)	36 (12)
Speed et al. weighted GRM	0.53 (0.09)	28 (10)	0.58 (0.12)	34 (14)
MAF-stratified approach	0.49 (0.06)	130 (42)	0.56 (0.05)	154 (28)

[a]Average ΔAIC between the null model (no GRM fitted) and the full model. A high ΔAIC indicates a better fit.
[b]The architecture letters match those in Table 1. The SD is over 50 replicates.

matched the simulation strategy (Table 2). The MAF-stratified approach gave a ΔAIC almost as high as those from the best model, despite the penalty from estimating more variance components. However, the ΔAICs from the weighted GRM method were consistently much lower, implying that the weighted GRM could not generate a good fit to the data and suggesting an inconsistency in the weighting strategy and the underlying assumption that allele effect sizes are drawn from the same distribution. The use of the Bayesian information criterion in place of the AIC made little difference to the conclusions drawn from the comparison between the MAF-stratified approach and the weighted method (Table S5). Moreover, the SD of estimates across replicates and SEs of estimates from within replicates (Table S6) were consistently higher, both undesirable properties. In contrast, the SD for the MAF-stratified approach was not much higher than that for standard GRM. We note that the difference between the estimates from the MAF-stratified approach and the Speed et al. method was significant given the values for SD in Table 2 (i.e., empirical SE is SD scaled by a square root of 50 [replicates]). When the majority of causal SNPs had a MAF < 0.1, the MAF approach generated the highest ΔAIC for var(allele effect size) ~ $[p_iq_i]^{-1}$ (strategy C). With var(allele effect size) ~ $[p_iq_i]^0$ (strategy D), the standard GRM gave the largest ΔAIC; however, the estimate was biased, demonstrating that the goodness-of-fit measure is not an ultimate indicator of the unbiasedness of the estimates and reflecting the penalty of estimating multiple parameters (five for the MAF-stratified approach versus one for the other methods) to goodness of fit. In principle, fitting more MAF bins could represent genetic architecture more accurately, but it brings the penalty of estimating more parameters. However, as sample sizes increase, it could become an increasingly appropriate strategy. In our simulations, results based on ten MAF bins were similar to those based on five MAF bins (Table S3). Lastly, bivariate methods for estimating SNP correlation between data from two independent data sets[14] have been proposed. Using simulated data, we investigated estimation of SNP correlation and found estimates to be robust to both genetic architecture and the GRM method (Table S7).

In applications to genome-wide SNP data from a schizophrenia case-control study,[13] we found that the differences between the estimates based on the GRM calculated with $s = -1$ or $s = 0$ or the MAF-stratified approaches were less extreme than those shown in the simulation scenarios, as shown in Table 3 for SNP heritability estimated with the real phenotype allocations (i.e., 2,928 schizophrenia cases

Table 3. SNP-Heritability Estimates from Different GRM Methods for 2,928 Schizophrenia Cases and 4,373 Controls from the Swedish Genome-wide Association Study Imputed to 1000 Genomes

GRM Method	h^2_{CC} (SE) Observed Scale	h^2_{SNP} (SE) Liability Scale[a]	ΔAIC[b]
Standard GRM with $s = -1$	0.57 (0.05)	0.33 (0.03)	143.88
Standard GRM with $s = 0$	0.49 (0.04)	0.28 (0.02)	151.26
Speed et al. weighted GRM	0.79 (0.10)	0.45 (0.06)	61.32
Speed et al. weighted GRM with buffer[c] = 1,000	0.79 (0.10)	0.45 (0.06)	62.00
MAF-stratified approach	0.52 (0.05)	0.30 (0.03)	148.50

[a]Assumes a disease prevalence of 0.01.
[b]ΔAIC between the null model (no GRM fitted) and the full model. A high ΔAIC indicates a better fit.
[c]In the weighting method, windows of 3,000 SNPs plus buffers of 500 SNPs were used by default in the LDAK software; in this example, the buffer size was increased to 1,000 SNPs.

and 4,373 controls) versus the genotype data used in the simulations. In this example, reflecting dense genotyping, the weighted GRM provides a much poorer fit to the data (smallest ΔAIC) and, according to our simulation results, most likely provides an overestimate of SNP heritability. The ΔAIC suggests that the GRM with $s = 0$ is the best fit to the data, implying relative importance of variance attributable to common SNPs.

The weighting method can be optimized by several alternative strategies. Taking into account the SNP density across MAF could improve the overcorrecting problem for rare variants (e.g., Table S1). The length and buffer size of the genomic segments (segments considered simultaneously within each window across the genome) in LDAK[1] should be optimized for the context of dense genotyping, although we did not observe a significant improvement when the number of buffers increased (from 500 to 1,000, which was suggested for dense genotyping with LDAK, Table 3). Moreover, these kinds of optimizations could be time consuming, computationally demanding, and sensitive to different data structure.

Our results should be considered in the context of some limitations of our study. First, we note that our simulations assumed that dense genotypes are known without error. In real data sets, there is uncertainty associated with imputed genotypes, but investigating the impact of imputation error on SNP heritability is beyond the scope of this study and merits further investigation. Second, we assumed only polygenic models in the simulations. Although this is a reasonable assumption for the majority of human complex traits or common diseases, consideration of major gene models could be relevant to some diseases, particularly autoimmune diseases. We note that Speed et al.[1] investigated a scenario of uneven LD in regions harboring major genes, a scenario not specifically considered here given that our focus was sparse versus dense genotype data.

In conclusion, Speed et al.[1] elegantly demonstrated the general robustness of the estimation of h^2_{SNP} but showed that both standard and weighted GRM could generate biased results when the underlying genetic architecture of the trait deviates from genetic architecture implicitly assumed in its calculation. The weighted GRM performed better than the standard GRM under the strategies they tested; however, we have shown that this conclusion does not always hold. Moreover, the weighted GRM has undesirable properties of poor goodness of fit and high variability of estimates. We have shown that the MAF-stratified approach generates estimates with little bias and high goodness of fit across a range of underlying genetic architectures. Because high LD is only possible between SNPs with similar MAFs, the use of multiple GRMs based on SNPs in different MAF bins provides better "matching" of contributions from SNPs given the LD between them and does not assume that the effect-size distribution is constant across the allelic frequency spectrum. In applications using the standard GRM method with $s = -1$ (the default setting in GCTA), we commonly found that the h^2_{SNP} estimates from the standard GRM and the MAF-stratified approach were similar,[7,13,15] implying that the underlying genetic architecture for these traits does not differ substantially from that implicitly assumed in the calculation of the GRM. The MAF-stratified approach can be carried out with the GCTA[2] command "–mgrm" to fit multiple GRMs estimated on the basis of the sets of SNPs in MAF bins.

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Supplemental Data

Supplemental Data include seven tables and can be found with this letter online at http://www.cell.com/AJHG.

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Web Resources

The URLs for data presented herein are as follows:

GCTA, http://www.complextraitgenomics.com/software/gcta/
LDAK, http://www.ldak.org

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Response to Lee et al.: SNP-Based Heritability Analysis with Dense Data

To the Editor: In Speed et al.,[1] we identified two potential issues when performing SNP-based heritability estimation: (1) estimates of h^2 can be biased when the tagging of causal variants differs from that of the SNPs used for calculating the genomic-relationship matrix (GRM), and (2) the accuracy of h^2 estimates depends on how closely the assumed relationship between a causal variant's minor allele frequency (MAF) and effect size matches the true relationship (this relationship can be modeled with a scale parameter s, where the standard assumption is $s = -1$). To resolve the