Secure and federated linear mixed model association tests

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Abstract

Privacy-preserving algorithms for genome-wide association studies (GWAS) promise to facilitate data sharing across silos to accelerate new discoveries. However, existing approaches do not support an important class of methods known as linear mixed model (LMM) association tests or provide limited privacy protection, due to their high computational burden of LMM under the secure computation framework. Here we introduce SafeGENIE, our secure and federated approach to LMM-based association studies. We leverage recent advances in LMMs and secure computation to develop efficient distributed algorithms for LMMs that also provide formal privacy guarantees. Our results shows that SafeGENIE obtains accurate association test results comparable to an existing centralized algorithm (REGENIE), and achieves practical runtimes even for large datasets including tens of thousands of individuals. Our work provides insights into the design of secure and distributed algorithms for collaborative genomic studies.

1 Introduction

Genome-wide association studies (GWAS) have been a major driving force of genomics research [1, 2]. Ongoing efforts to amass large and diverse collections of genomic data, such as the All of Us Program [3] and the UK Biobank [4], will continue to bring new discoveries of genetic variants of biological and clinical importance. However, many of the existing genomic datasets are held in isolated repositories within national or organizational boundaries under strict data sharing limitations, presenting a key hurdle for collaborative research [4–6]. Achieving sufficient statistical power for rare diseases and underrepresented populations (e.g. admixed individuals) requires new strategies to facilitate sharing of genomic data across multiple data repositories.

To this end, recent studies have proposed a range of privacy-preserving solutions for GWAS. These works aim to allow analyses to be jointly performed on multiple parties' datasets without sharing the raw individual-level data, thus providing a path to circumvent regulatory restrictions. In particular, cryptographic approaches based on secure computation frameworks [7–10], such as homomorphic encryption (HE) [11, 12] and secure multiparty computation (MPC) [13], offer the strongest notions of data privacy, which state that any (encrypted) data that is externally shared by each party is statistically indistinguishable from random (under certain security assumptions, such as the parties do not collude in the case of MPC) [14]. Alternative approaches based on trusted execution environment (TEE) technology [15, 16] or distributed/federated algorithms [17, 18] have also been proposed, albeit providing weaker forms of privacy protection.

A key limitation shared by most existing solutions for privacy-preserving GWAS is that they consider simplified analysis workflows that do not reflect the current standard practice in genomics. Specifically, population stratification correction, a crucial step in GWAS for mitigating confounding effects arising from the implicit association between population structure in the study cohort and the target phenotype [19], has long been unaddressed by solutions for privacy-preserving GWAS until a recent work incorporated an approach based on principal components analysis (PCA) [13]. The gap between current solutions and practical workflows is in part due to the fact that existing techniques for privacy protection typically incur a computational overhead that grows with the complexity of the algorithm being implemented, which renders the task of securing the sophisticated algorithms for modern GWAS highly challenging. Overcoming this barrier is a necessary step to realize the full potential of emerging privacy techniques.

Linear mixed models (LMMs) are one of two main classes of methods in the literature for addressing population stratification in GWAS. The other is a more traditional PCA-based approach [20], where the top principal components of the genotype matrix are included as fixed-effect covariates in the statistical models of genetic association to control for global population structure. In contrast, LMMs view the ancestry-related effect on the phenotype as a *random* effect, whose covariance is determined by the genetic relatedness patterns in the study cohort, also estimated from the data. LMMs are known to be more effective at capturing cryptic relatedness and fine-grain population structure within the study cohort [21]. Further enabled by recent algorithmic advances on reducing the computational burden of LMM computation [21–23], LMMs are increasingly becoming the preferred approach for GWAS [24]. Unfortunately, little work exists in the literature on *privacy-preserving* LMM-based GWAS over distributed datasets, which we ascribe to the complexity of existing LMM algorithms and their high computational cost even with full access to the data. This is a severe bottleneck hindering the use of privacy-preserving techniques for GWAS in practice.

In this work, we present SafeGENIE (secure and federated REGENIE), a privacy-preserving algorithm for performing LMM-based association tests on distributed genomic datasets. We develop a scalable algorithm for privacy-preserving LMM computation by synthesizing recent advances in cryptography, distributed algorithms, and population genetics, including: multiparty homomorphic encryption [25], distributed linear regression models [26], and an efficient stacked ridge regression approach for LMMs (called REGENIE [27]). SafeGENIE provides formal security guarantees offered by the underlying cryptographic frameworks, while maintaining efficiency by maximally leveraging local computation using plaintext (raw) data. Our work also incorporates new algorithmic strategies (e.g. based on linear algebra techniques for low-rank matrix updates) to overcome the unique computational bottlenecks that arise when jointly utilizing the aforementioned techniques in SafeGENIE. To our knowledge, SafeGENIE is the first privacy-preserving algorithm to fully implement the LMM-based GWAS pipeline.

Our experimental results show that SafeGENIE produces LMM association statistics closely matching those of the plaintext algorithm, demonstrating its utility for real-world studies. SafeGENIE also maintains

runtimes on the order of days for datasets including up to tens of thousands of individuals and is efficient in memory usage. Although this reflects the heavy computational burden of the underlying LMM computation, we show that our method is a significant improvement over the naïve baseline approaches and can be readily applied to many existing datasets. Our work represents a step toward enabling a wide range of genomic analyses to be performed while protecting the privacy of the data.

2 Problem Definitions and Review of Existing Methods

2.1 Linear Mixed Model (LMM) Association Studies

We start by formally describing the LMMs used for genome-wide association tests. LMMs model the target phenotype vector $\mathbf{y}$ of length N using the following linear model

$$\mathbf{y} = \beta_{\text{test}}\mathbf{x}_{\text{test}} + \mathbf{Z}^T\boldsymbol{\alpha} + \mathbf{g} + \mathbf{e},$$

where $\mathbf{x}_{\text{test}}$ is a vector of allele dosages of the variant being tested across N individuals, $\mathbf{Z}$ is a N-by-C matrix of observed covariates, $\mathbf{g}$ represents the ambient genetic effect, and $\mathbf{e}$ represents the environmental effect. Both $\mathbf{x}_{\text{test}}$ and $\mathbf{y}$ are standardized to have zero mean and unit variance. We let N and M be the number of individuals and the number of variants in the dataset, respectively.

In this model, β_{test} and $\boldsymbol{\alpha}$ describe the fixed effect sizes associated with the tested variant and the covariates, respectively, whereas $\mathbf{g}$ and $\mathbf{e}$ are modeled as random effects (hence the term "mixed" model). Under the standard infinitesimal model, which posits that the genetic effect on phenotype consists of many small effect-size variants, we can express

$$\mathbf{g} = \mathbf{X}_{\text{LOCO}}\boldsymbol{\beta}$$

where $\mathbf{X}_{\text{LOCO}}$ is a N-by-M_{LOCO} matrix consisting of the standardized genotypes of M_{LOCO} variants used to model the genetic effect based on the standard leave-one-chromosome-out (LOCO) scheme, which excludes all variants in the same chromosome as the tested variant in order to avoid the effects of linkage disequilibrium. These ambient variants are associated with effect sizes $\boldsymbol{\beta} \sim \mathcal{N}(\mathbf{0}, (\sigma_g^2/M_{\text{LOCO}})\mathbf{I}_{M_{\text{LOCO}}})$, inducing a distribution over the genetic effect as $\mathbf{g} \sim \mathcal{N}(0, \sigma_g^2\mathbf{K})$. $\mathbf{K} = \mathbf{X}_{\text{LOCO}}\mathbf{X}_{\text{LOCO}}^T/M_{\text{LOCO}}$ is referred to as the genetic relatedness or empirical kinship matrix. The environmental effect is modeled as $\mathbf{e} \sim \mathcal{N}(0, \sigma_e^2\mathbf{I}_N)$. Note that σ_g and σ_e represent the variances of the polygenic and environmental components. The goal of the association test is to test the null hypothesis $H_0 : \beta_{\text{test}} = 0$.

A standard technique [21,27] is to project the covariates out of the phenotypes and genotypes to simplify the computation. This results in a modified model

$$\tilde{\mathbf{y}} = \beta_{\text{test}}\tilde{\mathbf{x}}_{\text{test}} + \tilde{\mathbf{X}}_{\text{LOCO}}\boldsymbol{\beta} + \mathbf{e}, \tag{1}$$

where $\tilde{\mathbf{y}} = \mathbf{P}\mathbf{y}$, $\tilde{\mathbf{x}} = \mathbf{P}\mathbf{x}$, and $\tilde{\mathbf{X}} = \mathbf{P}\mathbf{X}$ with $\mathbf{P} = \mathbf{I}_N - \mathbf{Z}(\mathbf{Z}^T\mathbf{Z})^{-1}\mathbf{Z}^T$. Note that $\mathbf{P}$ projects a vector onto the null space of $\mathbf{Z}$.

The LMM χ^2 test statistic is given by

$$\chi^2 = \frac{(\tilde{\mathbf{x}}_{\text{test}}^T\mathbf{V}_{\text{LOCO}}^{-1}\tilde{\mathbf{y}})^2}{\tilde{\mathbf{x}}_{\text{test}}^T\mathbf{V}_{\text{LOCO}}^{-1}\tilde{\mathbf{x}}_{\text{test}}}, \tag{2}$$

where $\mathbf{V}_{\text{LOCO}} = \hat{\sigma}_g^2\mathbf{K} + \hat{\sigma}_e^2\mathbf{I}_N$ given the estimates $\hat{\sigma}_g$ and $\hat{\sigma}_e$ of the variance parameters.

2.2 Review of REGENIE: Efficient Stacked Regression for LMMs

Computing the LMM association statistics is a computationally expensive task, in part because the maximum likelihood estimation of the variance parameter σ_g involves costly matrix operations involving the $N \times N$ genetic relatedness matrix (GRM), which becomes prohibitively large for large-scale datasets. Much of the prior algorithmic development efforts have focused on speeding up the use of GRM, e.g. by exploiting a factorization of the matrix [23]. A recent algorithm called REGENIE [27] introduced a different strategy based on *stacked regression*, resulting in significant scalability improvements for LMM-based association tests,

while achieving comparable accuracy to existing state-of-the-art tools such as BOLT-LMM [21], fastGWA [22], and SAIGE [28]. Moreover, we discovered that REGENIE's approach is more amenable to efficient computation over distributed datasets, thereby forming an important basis for our SafeGENIE method.

In REGENIE [27], the whole-genome regression model in Equation 1 is estimated in two phases by first regressing out the contribution of $\tilde{\mathbf{X}}_{\text{LOCO}}$ from $\tilde{\mathbf{y}}$, then fitting β_{test} on the residuals to test for association. To further reduce the cost of regression over the large genome-wide matrix, REGENIE employs a stacked regression approach in the following two steps, referred to as Levels 0 and 1.

Level 0. The genotype matrix is first split into B contiguous blocks of T variants:

$$\tilde{\mathbf{X}}_{\text{LOCO}} = (\tilde{\mathbf{X}}^{(1)}_{\text{LOCO}}, \tilde{\mathbf{X}}^{(2)}_{\text{LOCO}}, \ldots, \tilde{\mathbf{X}}^{(B)}_{\text{LOCO}}).$$

Then for each block $b \in [B]$ and different choices of the regularization parameter $\lambda_r \in \{\lambda_1, \ldots, \lambda_R\}$ the following solution to the ridge regression problem $\tilde{\mathbf{y}} \approx \tilde{\mathbf{X}}^{(b)}_{\text{LOCO}}\boldsymbol{\beta}$ is computed.

$$\hat{\boldsymbol{\beta}}^{(b)}_{\lambda_r} := ((\tilde{\mathbf{X}}^{(b)}_{\text{LOCO}})^T\tilde{\mathbf{X}}^{(b)}_{\text{LOCO}} + \lambda_r\mathbf{I}_N)^{-1}(\tilde{\mathbf{X}}^{(b)}_{\text{LOCO}})^T\tilde{\mathbf{y}}, \tag{3}$$

$$\hat{\mathbf{y}}^{(b,r)}_{\text{LOCO}} := \tilde{\mathbf{X}}^{(b)}_{\text{LOCO}}\hat{\boldsymbol{\beta}}^{(b)}_{\lambda_r}. \tag{4}$$

The $\hat{\mathbf{y}}^{(b,r)}_{\text{LOCO}}$ is referred to as the predictors, representing the best polygenic prediction of the phenotype within a given genomic region, accounting for genotype correlations.

Level 1. The local predictors from Level 0 are aggregated to form a N-by-BR global feature matrix

$$\mathbf{W} := (\hat{\mathbf{y}}^{(1,1)}_{\text{LOCO}}, \ldots, \hat{\mathbf{y}}^{(B,R)}_{\text{LOCO}}). \tag{5}$$

Then another around of ridge regression is performed (with K-fold cross validation to choose the optimal regularization parameter η) to obtain the following genome-wide phenotype predictions:

$$\hat{\mathbf{y}}_{\text{LOCO}} := \mathbf{W}(\mathbf{W}^T\mathbf{W} + \eta\mathbf{I}_N)^{-1}\mathbf{W}\tilde{\mathbf{y}}. \tag{6}$$

Given this global predictor as a proxy for ambient genetic effect, the χ^2 statistic (with one degree of freedom) for the variant being tested in Equation 2 can now be formulated as

$$\chi^2 = \frac{(\tilde{\mathbf{x}}^T_{\text{test}}(\tilde{\mathbf{y}} - \hat{\mathbf{y}}_{\text{LOCO}}))^2}{\hat{\sigma}^2_e \cdot (\tilde{\mathbf{x}}^T_{\text{test}}\tilde{\mathbf{x}}_{\text{test}})}, \tag{7}$$

where $\hat{\sigma}^2_e = \|\tilde{\mathbf{y}} - \hat{\mathbf{y}}_{\text{LOCO}}\|^2_2/(N - C)$ is the estimated variance of the environmental effect.

The above approach substantially improves the speed of LMM computation by decomposing the problem into B separate local ridge regression problems, which can be performed in parallel in high performance computing environments. Importantly, by formulating the problem as a series of ridge regression tasks, the problem becomes more tractable for secure distributed computation, an aspect we exploit in our design of SafeGENIE to achieve efficiency.

2.3 Review of Privacy-Preserving GWAS Algorithms and Their Limitations

Prior works have developed privacy-aware algorithms for conducting GWAS over private datasets to facilitate genomic data sharing and collaboration. These methods leverage a range of different computational techniques with different strengths and weaknesses. Methods based on cryptographic frameworks such as secure multiparty computation (MPC) [7,29] and homomorphic encryption (HE) [9,30] aim to directly allow computation over encrypted data. MPC relies on interactive protocols among multiple parties to carry out the joint computation without revealing the private data, whereas HE enables non-interactive computation over the ciphertexts, albeit incurring higher computational overhead. GWAS algorithms based on both approaches have been developed [11–13], but they do not support LMM-based analyses. Another branch of methods follow a distributed or federated algorithm design [17,18], leveraging local computation performed

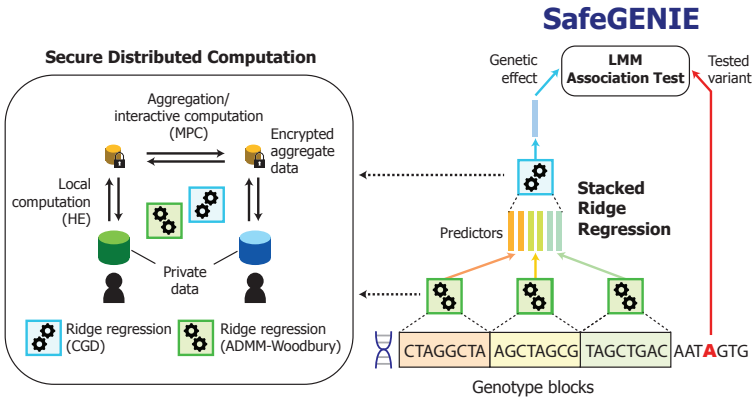

Figure 1: **Overview of SafeGENIE.** SafeGENIE implements a stacked ridge regression approach [27] to LMM association testing, whereby regression models trained on local genomic blocks are combined in another round of regression to produce estimated background genetic effects for the association tests. Both levels of ridge regression are performed using secure distributed algorithms we developed (CGD and ADMM-Woodbury), which leverage both homomorphic encryption and secure multiparty computation frameworks to provide privacy protection.

by each party on their respective dataset combined with aggregation steps that exchange information among the parties to move towards a global solution. Although these methods enjoy higher computational flexibility and efficiency compared to cryptographic approaches, there is a general lack of understanding of the extent to which private information is leaked in the intermediate results shared among the parties, thus providing limited privacy protection. Notably, a recent work in this line presented a promising solution for distributed training of generalized LMMs, which is closely related to our work. However, we note that the prior method did not address association testing and supports only a single covariate, thus the LMM-based GWAS remains an open problem. Approaches based on trusted execution environments, such as the Intel SGX enclave, have also been proposed [15, 16]. They perform computation on private data securely within a secure hardware component that is isolated from the rest of the host operating system. Similar to the plaintext distributed approach, these methods are efficient but offers limited privacy protection due to various security vulnerabilities that security researchers continue to discover, necessitating careful mitigation strategies (e.g. [31]). In this work, we adopt the cryptographic paradigm for secure computation, which offers the strongest notion of privacy, and focus on efficient algorithm design to address the associated computational burden.

3 Our Method: SafeGENIE

3.1 Overview of SafeGENIE

SafeGENIE is a privacy-preserving algorithm for LMM association analysis, which jointly analyzes private datasets held by different entities without leaking individual-level information. The results of SafeGENIE, by design, closely match those of running REGENIE on a pooled dataset with minimal loss in precision, while additionally protecting data privacy. The core computational framework of SafeGENIE is a hybrid of secure multiparty computation (MPC) and homomorphic encryption (HE), building upon the recently introduced framework of multiparty homomorphic encryption (MHE) [25, 32–34]. Combining the ability of HE to perform non-interactive secure computation at each site with efficient MPC protocols for high-complexity operations such as comparison and inverse square root [13], our hybrid approach enables SafeGENIE to maximally utilize local plaintext computation while maintaining flexibility and accuracy in computational capabilities. Using these cryptographic tools, SafeGENIE implements our distributed algorithm for stacked regression for LMMs, inspired by the success of the centralized plaintext algorithm introduced by REGENIE. We provide a graphical illustration of SafeGENIE in Figure 1.

3.2 Our Secure Computation Model

In our application setting, we consider P independent parties, each with a local GWAS dataset, who wish to jointly perform LMM association analysis on the pooled data without revealing private data. Our core approach is to keep these local datasets in plaintext and to encrypt, using MHE, only the intermediate results that need to be aggregated across the parties. MHE [25] is an extension of homomorphic encryption (HE) schemes where the decryption key is split among multiple parties using secret sharing, which ensures that encryption and homomorphic operations (performing computation over the secrets without decrypting the data) can be performed locally, while decryption requires all parties to cooperate, thus giving each party control over which pieces of results (such as the final association statistics) are revealed to other parties.

Importantly, MHE enables our distributed approach to secure computation, where we iterate between (1) a local computation phase, where each party computes local results leveraging both local plaintext data and encrypted shared data, and (2) an aggregation phase, where the parties interact to update the encrypted shared data, to perform the desired analysis. We additionally incorporate secret sharing-based MPC routines into our protocol by securely switching data representation between HE and secret shares. Secret shared data allow us to leverage efficient interactive protocols for more complex operations at the expense of higher communication. In our protocols, we securely perform comparison, inverse square root, and eigendecomposition over a small matrix using interactive MPC subroutines, while relying on HE for the rest. Note that, following the prior work on MPC-based GWAS [13], we adopt an efficient server-aided model for MPC, in which a coordinating party facilitates the computation by supplying the main parties with random numbers satisfying a certain structure. The coordinating party does not receive any portion of the private data other than the knowledge of data dimensions.

For the purposes of describing our distributed LMM algorithm implemented in SafeGENIE, we view our secure computation framework as a collection of building block protocols, each implementing a simple operation such as matrix multiplication or square root, which we compose to implement an end-to-end secure protocol that implements the LMM computation. As the focus of this work is on distributed algorithm design, in particular on optimizing the use of secure subroutines to efficiently perform LMM computation, we refer to relevant prior works on MPC and MHE for detailed descriptions of the subroutines used in SafeGENIE [12, 13].

3.3 Key Challenges of Distributed LMM Computation

To motivate our algorithmic techniques, we first describe the computational challenges in distributing the LMM computation. Recall that state-of-the-art LMM-based GWAS algorithms (e.g. BOLT-LMM [21]) account for population stratification by using the N-by-N genetic relatedness matrix (GRM) $\mathbf{K}$, which intuitively captures how individuals within a dataset are related to one another. A core computational step in the estimation of variance parameters or the calculation of association statistics is calculating a quantity of the form

$$(\mathbf{K} + \lambda \mathbf{I}_N)^{-1}\mathbf{v} = (\tilde{\mathbf{X}}\tilde{\mathbf{X}}^T/M + \lambda \mathbf{I}_N)^{-1}\mathbf{v}, \tag{8}$$

for some length-N vector $\mathbf{v}$. Because the size of $\mathbf{K}$ scales with the number of individuals in the dataset, for large-scale GWAS, this computation inherently incurs an overwhelming computational cost. As such, addressing this challenge has been the focus of recent algorithmic development efforts for LMM.

In our setting, the fact that the off-diagonal blocks of $\mathbf{K}$ describe relatedness between individuals in *different* collaborating sites introduces a unique difficulty in distributing the computation. When naïvely implemented, those interactive terms in $\mathbf{K}$ are bound to require heavy communication among parties to account for their contributions. Even recently proposed iterative approaches for efficiently solving this linear system of equations without the inverse (e.g. conjugate gradient descent used by BOLT-LMM [21]) presents a similar challenge, as it involves repeated multiplications of $\mathbf{K}$ with a candidate solution vector. Moreover, we note that $\mathbf{K}$ is typically defined over covariate-corrected genotypes $\tilde{\mathbf{X}} = \mathbf{P}\mathbf{X}$, where $\mathbf{P}$ denotes a projection matrix for removing the covariate effect, which introduces another layer of entanglement between the private datasets at different sites, making distributed computation further challenging.

3.4 Our Approach: Secure Distributed Ridge Regression with Covariates

SafeGENIE approaches this problem differently. Following the methodology of REGENIE [27], instead of using the notion of a GRM, we train ridge regression models for local genomic windows to use as a proxy for ambient genetic effect on phenotype. Correcting for these polygenic predictions by testing for a variant's association with the phenotype residuals, our approach implicitly accounts for population stratification under the LMM formulation.

Our work identifies this alternative approach for LMMs as a key enabling factor for distributing the computation. Let $\tilde{\mathbf{X}}^{(b)}$ be a subset of columns from a genotype matrix corresponding to a genomic block with M_b variants. The ridge regression problem for LMM reduces to computing the expression

$$((\tilde{\mathbf{X}}^{(b)})^T\tilde{\mathbf{X}}^{(b)} + \lambda\mathbf{I}_{M_b})^{-1}(\tilde{\mathbf{X}}^{(b)})^T\tilde{\mathbf{y}}. \tag{9}$$

In contrast to Equation 8, we see that the inverse operation is for a matrix of size M_b-by-M_b, which is significantly smaller than $\mathbf{K}$ (note M_b is typically 1000). Furthermore, for horizontally distributed $\tilde{\mathbf{X}}^{(b)}$, where each party p holds a subset of rows in this matrix denoted $\tilde{\mathbf{X}}_p^{(b)}$, we have the following decomposition

$$(\tilde{\mathbf{X}}^{(b)})^T\tilde{\mathbf{X}}^{(b)} = \sum_{p=1}^{P}(\tilde{\mathbf{X}}_p^{(b)})^T\tilde{\mathbf{X}}_p^{(b)}. \tag{10}$$

This property allows SafeGENIE to distribute the computation more efficiently across the parties and maximally leverage plaintext data that is available locally. In the following section, we describe how we exploit this insight to design secure and distributed algorithms for conjugate gradient descent (CGD) and alternating direction method of multipliers (ADMM) approaches for ridge regression, which are used by SafeGENIE to carry out the Level 1 and Level 0 steps of REGENIE, respectively.

3.5 SafeGENIE Algorithm Details

Recall from Section 2.2 that stacked regression approach to LMM involves solving the following two ridge regression problems in Levels 0 and 1.

$$\hat{\boldsymbol{\beta}}_{\lambda_r}^{(b)} := ((\tilde{\mathbf{X}}_{\text{LOCO}}^{(b)})^T\tilde{\mathbf{X}}_{\text{LOCO}}^{(b)} + \lambda_r\mathbf{I}_N)^{-1}(\tilde{\mathbf{X}}_{\text{LOCO}}^{(b)})^T\tilde{\mathbf{y}}, \qquad \textbf{(Level 0)} \tag{11}$$

$$\hat{\mathbf{y}}_{\text{LOCO}} := \mathbf{W}(\mathbf{W}^T\mathbf{W} + \eta\mathbf{I}_N)^{-1}\mathbf{W}\tilde{\mathbf{y}}. \qquad \textbf{(Level 1)} \tag{12}$$

The first is solved KBR times for each pair of block b and regularization parameter λ_r using K -fold cross validation, and the second is solved KR times for each of R values of η using the same K-fold cross validation. The challenging step in both is the multiplication by the inverse matrix, which is infeasible to solve directly when the matrix is only available in encrypted form. This is unlike REGENIE, which explicitly solves for the inverse using eigenfactorization. Explicitly computing the inverse for a large, homomorphically encrypted matrix imposes a considerable computational burden, which we aim to avoid. To address this, we develop two algorithms described below.

3.5.1 Secure Distributed Conjugate Gradient Descent (CGD)

Conjugate Gradient Descent (CGD) [35] is a well-known iterative algorithm for solving a system of linear equations without explicitly constructing the inverse of the design matrix. Notably, BOLT-LMM heavily utilizes the CGD algorithm to avoid working with the inverse of GRM. A requirement of CGD is that the design matrix be positive definite; in our setting, the regularization term in ridge regression ensures this property. Hence, CGD can be applied to any of the ridge regression problems in our task. The central step in CGD is a multiplication of a candidate solution vector with the design matrix (not the inverse), which lends itself to efficient distributed computation. We outline our distributed CGD algorithm in Algorithm 1.

We highlighted in blue the modified step in the distributed approach. As explained in Section 3.4, the fact that the design matrix $\mathbf{A}^T\mathbf{A}$ in our setting decomposes as a sum of local design matrices $\mathbf{A}_p^T\mathbf{A}_p$ allows this step to be performed independently, then aggregated after both multiplications (the SumAggregate step). Thus, the required communication scales with the number of predictive features (variants), not the number

Algorithm 1 Distributed Conjugate Gradient Descent for Ridge Regression

Input: Number of parties P, horizontally distributed input matrix $\mathbf{A} = [\mathbf{A}_1^T, \ldots, \mathbf{A}_P^T]^T$, target vector $\mathbf{b}$, regularization parameter λ, number of iterations τ.
Output: A vector $\mathbf{x}$ that satisfies $(\mathbf{A}^T\mathbf{A} + \lambda\mathbf{I})\mathbf{x} \approx \mathbf{b}$.

Initialize: $\mathbf{x}_0 \leftarrow \mathbf{0}$, $\mathbf{y}_0 \leftarrow \mathbf{b}$, $\mathbf{r}_0 \leftarrow \mathbf{b}$
for $k \in \{0, \ldots, \tau - 1\}$ **do**
  Each party p locally computes $\mathbf{z}_p \leftarrow \mathbf{A}_p^T\mathbf{A}_p\mathbf{y}_k$
  $\mathbf{z} \leftarrow \mathsf{SumAggregate}(\{\mathbf{z}_1, \ldots, \mathbf{z}_P\})$
  $\mathbf{u} \leftarrow \mathbf{z} + \lambda\mathbf{y}_k$ ▷ $\mathbf{u} = (\mathbf{A}^T\mathbf{A} + \lambda\mathbf{I})\mathbf{y}_k$
  $\alpha \leftarrow (\mathbf{r}_k^T\mathbf{r}_k)/(\mathbf{y}_k^T\mathbf{z})$
  $\mathbf{x}_{k+1} \leftarrow \mathbf{x}_k + \alpha\mathbf{y}_k$
  $\mathbf{r}_{k+1} \leftarrow \mathbf{r}_k - \alpha\mathbf{z}$
  $\beta \leftarrow (\mathbf{r}_{k+1}^T\mathbf{r}_{k+1})/(\mathbf{r}_k^T\mathbf{r}_k)$
  $\mathbf{y}_{k+1} \leftarrow \mathbf{r}_k + \beta\mathbf{y}_k$
end for
return $\mathbf{x}_\tau$

of samples held by each party, thereby offering better scaling to large datasets. To apply this algorithm to encrypted datasets, each of the calculations, namely matrix-vector multiplication, inner products, and addition/subtraction, are implemented using HE routines, with the exception of division, for which we switch to a secret sharing-based MPC routine. Note that the SumAggregate step involves each party broadcasting their share to others and adding up all shares (homomorphically), which does not involve any decryption. For efficiency, this procedure is implemented over a star network where a central coordinator aggregates all data and in turn relays the result to all parties.

3.5.2 Secure ADMM for Ridge Regression with Covariates

Although CGD offers a natural distributed solution for ridge regression, it is still computationally burdensome for large input matrices. For instance, consider applying CGD to Level 0 of REGENIE, where the input

$$\mathbf{A} = \tilde{\mathbf{X}}^{(b)} = [(\tilde{\mathbf{X}}_1^{(b)})^T, \ldots, (\tilde{\mathbf{X}}_P^{(b)})^T]^T. \tag{13}$$

When each party performs the following local computation in Algorithm 1

$$\mathbf{z}_p \leftarrow (\tilde{\mathbf{X}}_p^{(b)})^T\tilde{\mathbf{X}}_p^{(b)}\mathbf{y}_k, \tag{14}$$

they first need to multiply $\mathbf{y}_k$ with $\tilde{\mathbf{X}}_p^{(b)}$, which has an output dimension of N_p (number of individuals in party p's dataset), followed by another multiplication with $(\tilde{\mathbf{X}}_p^{(b)})^T$, finally resulting in a vector of length M_b. This is due to the fact that $(\tilde{\mathbf{X}}_p^{(b)})^T\tilde{\mathbf{X}}_p^{(b)}$ cannot be precomputed in plaintext, since $\tilde{\mathbf{X}}_p^{(b)}$ requires covariate correction involving all parties covariate data. Note that M_b is a user parameter typically set to a small value (e.g. 1000) whereas N_p can grow much larger for large-scale datasets. Therefore, CGD does not benefit from any dimension reduction (to M_b) that is otherwise exhibited in the plaintext formulation.

SafeGENIE overcomes this challenge by leveraging the alternating direction method of multipliers (ADMM) technique [36], which is a powerful method for transforming convex optimization problems into distributed optimization problems that can be more efficiently solved. Intuitively, ADMM relaxes the global objective by decoupling the terms involving each individual dataset, which in turn can be jointly optimized using local update equations that, in our case, involve plaintext matrices of size M_b as desired. Our techniques draw inspiration from a recent work in security literature, which introduced a secure multiparty ADMM algorithm for distributed linear regression [26]. Our work extends this work to the setting where the design matrix must be covariate-corrected, which introduces additional challenges as we describe below.

Here we describe how we apply ADMM to the ridge regression problem in Level 0 of REGENIE. Recall that the ridge regression of $\tilde{\mathbf{y}}$ onto $\tilde{\mathbf{X}}^{(b)}$ with regularization parameter λ can be equivalently formulated as the following optimization problem:

$$\text{minimize}_{\mathbf{w}} \quad \frac{1}{2}\|\tilde{\mathbf{X}}^{(b)}\mathbf{w} - \tilde{\mathbf{y}}\|_2^2 + \frac{1}{2}\lambda\|\mathbf{w}\|_2^2. \tag{15}$$

To apply ADMM, we first decouple the two terms using a slack variable $\mathbf{z}$ with an equality constraint as follows.

$$\text{minimize}_{\mathbf{w},\mathbf{z}} \quad \frac{1}{2}\|\tilde{\mathbf{X}}^{(b)}\mathbf{w} - \tilde{\mathbf{y}}\|_2^2 + \frac{1}{2}\lambda\|\mathbf{z}\|_2^2, \tag{16}$$

$$\text{s.t.} \quad \mathbf{w} - \mathbf{z} = 0. \tag{17}$$

Next, we note that the first objective term can be written as a sum of squared loss computed over each party's dataset as

$$\|\tilde{\mathbf{X}}^{(b)}\mathbf{w} - \tilde{\mathbf{y}}\|_2^2 = \sum_{p=1}^{P} \|\tilde{\mathbf{X}}_p^{(b)}\mathbf{w} - \tilde{\mathbf{y}}_p\|_2^2, \tag{18}$$

where we partition $\tilde{\mathbf{y}} = [\tilde{\mathbf{y}}_1, \ldots, \tilde{\mathbf{y}}_P]$ in the same manner as $\tilde{\mathbf{X}}^{(b)}$. Finally, further decoupling the $\mathbf{w}$ parameters across parties for distributed optimization, we obtain

$$\text{minimize}_{\mathbf{w}_p,\mathbf{z}} \quad \frac{1}{2}\sum_{p=1}^{P} \|\tilde{\mathbf{X}}_p^{(b)}\mathbf{w}_p - \tilde{\mathbf{y}}_p\|_2^2 + \frac{1}{2}\lambda\|\mathbf{z}\|_2^2, \tag{19}$$

$$\text{s.t.} \quad \mathbf{w}_p - \mathbf{z} = 0, \forall p. \tag{20}$$

The resulting iterative optimization procedure based on the standard ADMM derivation, for general local matrices $\mathbf{A}_1$,...,$\mathbf{A}_P$, is shown in Algorithm 2.

Algorithm 2 Standard ADMM Algorithm for Ridge Regression (adapted from [36])

Input: Number of parties P, horizontally distributed input matrix $\mathbf{A} = [\mathbf{A}_1^T, \ldots, \mathbf{A}_P^T]^T$, target vector $\mathbf{b} = [\mathbf{b}_1^T, \ldots, \mathbf{b}_P^T]^T$, regularization parameter λ, learning rate ρ, number of iterations τ.
Output: A vector $\mathbf{z}$ that satisfies $(\mathbf{A}^T\mathbf{A} + \lambda\mathbf{I})\mathbf{z} \approx \mathbf{b}$.

```
Each party p:
    Locally computes R_p^{-1} ← (A_p^T A_p + ρI)^{-1}
    Initializes w_p^0 ← 0, u_p^0 ← 0 and a global vector z^0 ← 0
for k ∈ {0, ..., τ − 1} do
    Each party p locally computes w_p^{k+1} ← R_p^{-1}(b + ρz^k − u_p^k)
    w̄^{k+1} ← SumAggregate({w_1^{k+1}, ..., w_P^{k+1}})/P
    ū^k ← SumAggregate({u_1^k, ..., u_P^k})/P
    Each party p locally computes:
        z^{k+1} ← (ρw̄^{k+1} + ū^k)/(λ/P + ρ)
        u_p^{k+1} ← u_p^k + ρ(w_p^{k+1} − z^{k+1})
end for
return z^τ
```

However, we note that our given $\mathbf{A}_p = \tilde{\mathbf{X}}_p^{(b)}$ is not available in plaintext, as it is meant to be standardized and covariate-corrected based on the global matrix $\tilde{\mathbf{X}}^{(b)}$. Therefore, although each party has access to their own raw genotype martix $\mathbf{X}_p^{(b)}$, they are not able to precompute the following matrix shown in Algorithm 2 in plaintext:

$$\mathbf{R}_p^{-1} = ((\tilde{\mathbf{X}}_p^{(b)})^T\tilde{\mathbf{X}}_p^{(b)} + \rho\mathbf{I}_{M_b})^{-1}. \tag{21}$$

In SafeGENIE, we introduce a technique to resolve this issue by using the Woodbury matrix identity [37] to perform covariate correction in the computation of $\mathbf{R}_p^{-1}$ on the fly as follows. First, recall that

$$\tilde{\mathbf{X}}^{(b)} = (\mathbf{I}_N - \mathbf{Z}(\mathbf{Z}^T\mathbf{Z})^{-1}\mathbf{Z}^T)\mathbf{X}^{(b)}\mathbf{S}^{(b)}, \tag{22}$$

where $\mathbf{Z}$ is an N-by-C covariate matrix, and $\mathbf{S}$ represents a diagonal matrix with inverse standard deviations for each column of $\mathbf{X}^{(b)}$. We include an all-ones vector as a covariate in $\mathbf{Z}$, which implicitly accounts for mean centering of $\mathbf{X}^{(b)}$. With one round of aggregation, we precompute a small C-by-M_b matrix

$$\mathbf{H}^{(b)} = \mathbf{Z}^T\mathbf{X}^{(b)} = \sum_{p=1}^{P} \mathbf{Z}_p^T\mathbf{X}_p^{(b)}, \tag{23}$$

where each summand is computed locally using plaintext matrices then aggregated in an encrypted form. Next, noting that

$$\tilde{\mathbf{X}}^{(b)} = (\mathbf{X}^{(b)} - \mathbf{Z}(\mathbf{Z}^T\mathbf{Z})^{-1}\mathbf{H}^{(b)})\mathbf{S}^{(b)}, \tag{24}$$

we are able to express

$$\mathbf{R}_p^{-1} = \mathbf{S}^{-1}(([(\mathbf{X}_p^{(b)})^T\mathbf{X}_p^{(b)} + \rho\mathbf{I}_{M_b}] + \mathbf{UCV})^{-1}\mathbf{S}^{-1}, \tag{25}$$

for some matrices $\mathbf{U}, \mathbf{V}^T \in \mathbb{R}^{M_b \times 2C}$ and $\mathbf{C} \in \mathbb{R}^{2C \times 2C}$ (see Appendix for full derivation; note the inner dimension of $2C$). Finally, using the Woodbury identity and letting $\mathbf{B} := (\mathbf{X}_p^{(b)})^T\mathbf{X}_p^{(b)} + \rho\mathbf{I}_{M_b}$ to simplify the notation, we can expand the inverse as

$$(\mathbf{B} + \mathbf{UCV})^{-1} = \mathbf{B}^{-1} - \mathbf{B}^{-1}\mathbf{U}(\mathbf{C}^{-1} + \mathbf{VB}^{-1}\mathbf{U})^{-1}\mathbf{VB}^{-1}. \tag{26}$$

We have successfully reformulated the computation of $\mathbf{R}_p^{-1}$ as one involving an *inverse of a plaintext matrix* $\mathbf{B}$ and several matrix multiplications with a small inner dimension of $2C$. Note that the new composite inverse matrix $(\mathbf{C}^{-1} + \mathbf{VB}^{-1}\mathbf{U})^{-1}$ can be efficiently computed using secure MPC protocols, using the eigenfactorization routine introduced in prior work [13].

As a result, we can compute a key matrix $\mathbf{B}^{-1}$ completely locally in plaintext, then use Equations 7 and 2 to compute the multiplication with $\mathbf{R}_p^{-1}$ on the fly using the plaintext $\mathbf{B}^{-1}$. Note that this step is the only expensive matrix multiplication in the ADMM algorithm, and as such our reformulated ADMM offers significant reduction in computational cost. Moreover, we emphasize that, aside from the precomputation of $\mathbf{H}^{(b)}$ and $\mathbf{B}^{-1}$, none of the matrix operations in our ADMM algorithm scales with the number of individuals in the dataset, and thus scales very efficiently to datasets with many samples. Our final ADMM algorithm for ridge regression with covariates, leveraging the Woodbury identity technique, is presented in Algorithm 3 (changes with respect to the standard formulation are shown in blue).

Algorithm 3 Our Improved ADMM Algorithm for Ridge Regression with Covariates

Input: Number of parties P, horizontally distributed input matrix $\mathbf{X} = [\mathbf{X}_1^T, \ldots, \mathbf{X}_P^T]^T$ and a covariate matrix $\mathbf{Z} = [\mathbf{Z}_1^T, \ldots, \mathbf{Z}_P^T]^T$, a diagonal matrix $\mathbf{S}$ with inverse standard deviations of columns of $\mathbf{X}$, target vector $\mathbf{b} = [\mathbf{b}_1^T, \ldots, \mathbf{b}_P^T]^T$, regularization parameter λ, learning rate ρ, number of iterations τ.
Output: A vector $\mathbf{z}$ that satisfies $(\mathbf{A}^T\mathbf{A} + \lambda\mathbf{I})\mathbf{z} \approx \mathbf{b}$, where $\mathbf{A} := (\mathbf{I} - \mathbf{Z}(\mathbf{Z}^T\mathbf{Z})^{-1}\mathbf{Z}^T)\mathbf{XS}$

Each party p locally computes $\mathbf{H}_p \leftarrow \mathbf{Z}_p^T\mathbf{X}_p$
$\mathbf{H} \leftarrow \mathsf{SumAggregate}(\{\mathbf{H}_1, \ldots, \mathbf{H}_P\})$
Each party p:
  Initializes $\mathbf{w}_p^0 \leftarrow 0, \mathbf{u}_p^0 \leftarrow 0$ and a global vector $\mathbf{z}^0 \leftarrow 0$
  Locally computes $\mathbf{B}_p^{-1} \leftarrow (\mathbf{X}_p^T\mathbf{X}_p + \rho\mathbf{I}_{M_b})^{-1}$
Precompute $\mathbf{L}_p := (\mathbf{C}_p^{-1} + \mathbf{V}_p\mathbf{B}_p^{-1}\mathbf{U}_p)^{-1}$ in Equation 2 for all parties
for $k \in \{0, ..., \tau - 1\}$ **do**
  Each party p:
    Locally computes $\mathbf{h} \leftarrow \mathbf{B}_p^{-1}\mathbf{S}^{-1}(\mathbf{b} + \rho\mathbf{z}^k - \mathbf{u}_p^k)$
    Locally computes $\mathbf{w}_p^{k+1} \leftarrow \mathbf{S}^{-1}(\mathbf{h} - \mathbf{B}_p^{-1}\mathbf{U}_p\mathbf{L}_p\mathbf{V}_p\mathbf{h})$
  $\bar{\mathbf{w}}^{k+1} \leftarrow \mathsf{SumAggregate}(\{\mathbf{w}_1^{k+1}, \ldots, \mathbf{w}_P^{k+1}\})/P$
  $\bar{\mathbf{u}}^k \leftarrow \mathsf{SumAggregate}(\{\mathbf{u}_1^k, \ldots, \mathbf{u}_P^k\})/P$
  Each party p locally computes:
    $\mathbf{z}^{k+1} \leftarrow (\rho\bar{\mathbf{w}}^{k+1} + \bar{\mathbf{u}}^k)/(\lambda/P + \rho)$
    $\mathbf{u}_p^{k+1} \leftarrow \mathbf{u}_p^k + \rho(\mathbf{w}_p^{k+1} - \mathbf{z}^{k+1})$
end for
return $\mathbf{z}^\tau$

3.6 Computational Complexity of SafeGENIE

SafeGENIE greatly reduces the runtime of a direct implementation of REGENIE in a distributed setting. By using our improved ADMM algorithm, we delegate large matrix inverse operations to be performed locally in plaintext. Since in practice the overhead of cryptographic operations greatly overshadows that of plaintext computation, in our complexity analysis we only consider homomorphic operations over the encrypted data.

The implementation of ADMM with our Woodbury optimization is separated into two components, the precomputation of a small matrix inverse in the Woodbury identity and the main ADMM iterations. For the precomputation of the $\mathbf{L}_p$ matrix, each party performs a $T \times T$ matrix multiplication on the order of the number of covariates. Each main iteration is dominated by the work of multiplying a $T \times T$ plaintext matrix $\mathbf{B}_p^{-1}$ twice with a ciphervector, combined with cipher-cipher multiplications with precomputed matrices U, L, and V. Like in the plaintext setting, matrix vector multiplication in HE scales linearly with the size of the matrix. Since ridge regression in Level 0 is computed for each block, cross-validation fold, and regularization parameter, the complexity of Level 0 is $O(KBRT^2\tau)$ where τ is the number of iterations in ADMM. Since $M = BT$, this can be expressed as $O(KRMT\tau)$. We note that this is a much better asymptotic runtime than naively using CGD for Level 0. Each iteration of CGD scales linearly with the size of the matrix being multiplied, which is $N \times T$ in our case. Therefore, the total runtime of Level 0 with CGD is $O(KBRTN\tau)$, or equivalently $O(KRMN\tau)$, which is a factor of N/T larger than our ADMM method.

For Level 1, since we evaluate the CGD subroutine lazily without explicitly constructing the design matrix, we distribute the work in a way where each party multiplies their respective plaintext genotype matrix with a vector. Since the size of the matrix is $N \times BR$, and there are KR different ridge regression that must be performed, the runtime complexity of Level 1 is $O(KR^2NB\tau)$, where τ is the number of iterations in CGD, and K and R are small numbers (default values of 5 in REGENIE).

Lastly, to compute association statistics, much of the work can be done in plaintext. The 22 LOCO residual vectors that are generated for the association statistic pipeline must be covariate corrected and then multiplied by the associated snp blocks in the genotype matrix. Therefore, this is equivalent to be encapsulated by one full cipher plain matrix multiplication with all parties genotype matrices and a vector, resulting in a theoretical asymptotic complexity of $O(NM)$, however in practice since only one multiplication is needed, computing association statistics is the quickest of the three levels of computation.

3.7 Implementation Details

SafeGENIE is implemented using the distributed CKKS framework in Lattigo, which is an open source library in Golang for homomorphic encryption schemes. We extended the library by implementing secret sharing-based MPC functionalities based on our prior work [13]. In addition, SafeGENIE was implemented using Golang's built in multi-threading framework and networking protocols, which allow interactive computation over encrypted data to be performed in a parallel manner across multiple machines. Our implementation also features efficient streaming pipelines for accessing blocks of the genotype matrix, which helps ensures that the memory usage of the program stays low regardless of the size of the dataset.

4 Experimental Results

To demonstrate the performance of SafeGENIE on a real GWAS dataset, we obtained a dataset of 9,178 East Asian lung cancer patients (5,054) and control individuals (4,053) from the dbGaP repository (accesion phs000716.v1.p1). After a quality control filter excluding individuals with missingness rate higher than 10%, we retained 9,107 individuals. For accuracy comparison, we evaluated SafeGENIE based on a reduced genome-wide set of 10K single nucleotide polymorphisms (SNPs). Following the default parameter of REGENIE, we then divided the SNPs into 10 blocks to perform the stacked ridge regression. For the association tests, we applied a LOCO scheme at the block level, leaving out one genomic block at a time where the tested variant resides.

For experimental setup, we created three VM instances in the Goolge Cloud Platform, each with 128 RAM and 16 virtual CPUs, located in the same geographic zone. One VM served the role of a coordinating party for server-aided MPC routines, with the other two as main data holders participating in the collaborative LMM analysis. We split the GWAS data into two sets of individuals (4554 and 4553 individuals, respectively) and individually uploaded the corresponding genotype, phenotype, and covariate data to the two main parties' VMs. We then executed the SafeGENIE program with point-to-point communication channels between pairs of parties for interactive steps of the procotol.

Figure 2 shows the resulting LMM-based association statistics from SafeGENIE compared against the output from running REGENIE (obtained from `https://rgcgithub.github.io/regenie/`) on a pooled dataset. The Manhattan plots showing the genome-wide association signals are nearly identical between the

two approaches, suggesting that SafeGENIE successfully replicates the analysis performed by REGENIE in a centralized setting. Note that SafeGENIE never has access to the whole data in one site; it only jointly analyzes distributed datasets in a secure manner using our cryptographic protocols. We note that in this dataset a particularly strong association is identified for SNP rs6537539, which is associated with the *ERCC6* gene, a known cancer gene whose expression is up-regulated in non-small cell lung cancer (NSCLC) [38]. Quantitatively measuring the agreement between the two outputs resulted in a correlation coefficient of 0.993 (Figure 2C). We also observed a strong agreement in the genome-wide polygenic predictions of the phenotype (Figure 2D), which represent a key intermediate result in the LMM analysis.

The total runtime of SafeGENIE on this dataset was 3.9 hours with a communication of 181 GB. Most of the runtime as well as communication can be attributed to Level 0 (3.2 hours and 174 GB; compared to 0.7 hours and 4.7 GB of Level 1), which fits many local ridge regression models across genomic blocks. We note that this step is embarrassingly parallel and thus can be sped up with more cores. In contrast, a baseline CGD solution for Level 0 without our ADMM algorithm, is estimated to take 6.8 hours of runtime and 255 GB of communication. Our improvement is expected to be even greater at larger scales given our reduced dependence on N. Lastly, extrapolating our measurements give us the following estimates for larger datasets (assuming 500K variants): 23 hours ($N = 10K$), 52 hours ($N = 50K$) and 90 hours ($N = 100K$).

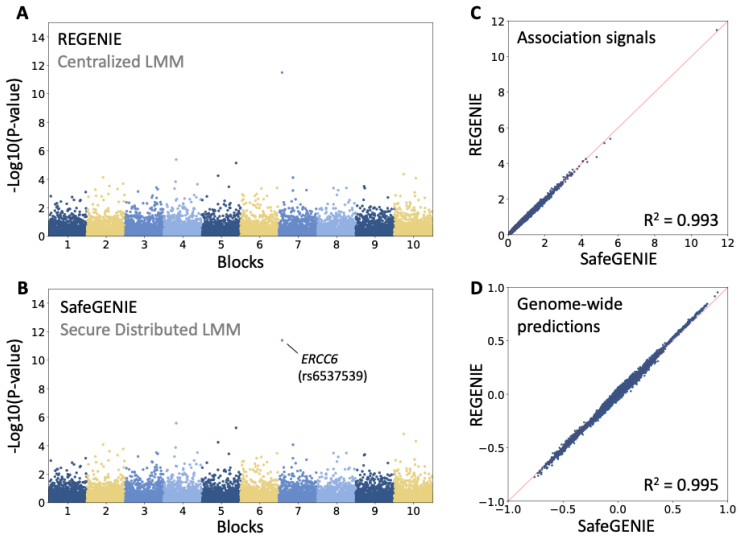

Figure 2: **SafeGENIE closely reproduces REGENIE association statistics while securely analyzing distributed datasets.** The Manhattan plot for SafeGENIE mirrors the Manhattan plot obtained from running the centralized REGENIE on the same lung cancer dataset (**A**, **B**). Subfigure **C** compares the negative log p-values for all variants in the dataset generated by REGENIE and by SafeGENIE. Subfigure **D** plots the genome-wide prediction vectors obtained by both methods before the association testing pipeline. Both show that the results from SafeGENIE are highly correlated to those of REGENIE with an R^2 value over 0.99 in both plots.

5 Discussion

We introduced SafeGENIE, a privacy-preserving and distributed approach to LMM association studies. Leveraging the insight that a recent stacked regression approach to LMM presents a path for efficient distributed computation, we developed efficient distributed algorithms for ridge regression with covariates for use as core routines in SafeGENIE. Our results show that SafeGENIE produces nearly identical association results compared to REGENIE, a centralized LMM algorithm, while demonstrating efficient runtime performance which is expected to remain in the order of days for large datasets including tens of thousands of individuals. Directions for future work include increasing the robustness of SafeGENIE to a wide range of parameter settings (e.g. including extreme values of variance estimates); and further developing methods to support other types of association tests based on LMM beyond the quantitative trait model addressed in this work. The insights offered by our work on how to design efficient distributed algorithms for secure computation are broadly applicable to enhancing privacy in other genomic analysis workflows.

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Appendix

Derivation of Improved ADMM based on the Woodbury Identity

To better exploit the power of ADMM, we aim to expand the following inverse.

$$\mathbf{R}_p^{-1} = ((\tilde{\mathbf{X}}_p^{(b)})^T \tilde{\mathbf{X}}_p^{(b)} + \rho \mathbf{I}_{M_b})^{-1}. \tag{1}$$

The Woodbury Matrix identity allows for the expansion of inverses into a new inverse with a small rank one update if the initial matrix is of the following form

$$(\mathbf{B} + \mathbf{UCV})^{-1} = \mathbf{B}^{-1} - \mathbf{B}^{-1}\mathbf{U}(\mathbf{C}^{-1} + \mathbf{VB}^{-1}\mathbf{U})^{-1}\mathbf{VB}^{-1}. \tag{2}$$

We can begin by expanding $\tilde{\mathbf{X}}_p^{(b)}$ into its components. Namely, we know that

$$\tilde{\mathbf{X}}^{(b)} = (\mathbf{X}^{(b)} - \mathbf{Z}(\mathbf{Z}^T\mathbf{Z})^{-1}\mathbf{H}^{(b)})\mathbf{S}^{(b)}. \tag{3}$$

Therefore,

$$\mathbf{R}_p^{-1} = (((\mathbf{X}^{(b)} - \mathbf{Z}(\mathbf{Z}^T\mathbf{Z})^{-1}\mathbf{H}^{(b)})\mathbf{S}^{(b)})^T(\mathbf{X}^{(b)} - \mathbf{Z}(\mathbf{Z}^T\mathbf{Z})^{-1}\mathbf{H}^{(b)})\mathbf{S}^{(b)} + \rho\mathbf{I}_{M_b})^{-1}, \tag{4}$$

After flipping the inner transpose, we get the following

$$\mathbf{R}_p^{-1} = (\mathbf{S}^{(b)}((\mathbf{X}^{(b)})^T - (\mathbf{H}^{(b)})^T(\mathbf{Z}^T\mathbf{Z})^{-1}\mathbf{Z}^T)(\mathbf{X}^{(b)} - \mathbf{Z}(\mathbf{Z}^T\mathbf{Z})^{-1}\mathbf{H}^{(b)})\mathbf{S}^{(b)} + \rho\mathbf{I}_{M_b})^{-1}, \tag{5}$$

After distribution the expression becomes

$$\mathbf{R}_p^{-1} = ((\mathbf{X}^{(b)})^T\mathbf{X}^{(b)} + \rho\mathbf{I}_{M_b} - (\mathbf{H}^{(b)})^T(\mathbf{Z}^T\mathbf{Z})^{-1}\mathbf{Z}^T\mathbf{X}^{(b)} - (\mathbf{X}^{(b)})^T(\mathbf{Z}^T\mathbf{Z})^{-1}\mathbf{H}^{(b)} + (\mathbf{H}^{(b)})^T(\mathbf{Z}^T\mathbf{Z})^{-1}\mathbf{Z}^T\mathbf{Z}(\mathbf{Z}^T\mathbf{Z})^{-1}\mathbf{H}^{(b)})^{-1},$$

We then consolidate two terms together.

$$\mathbf{R}_p^{-1} = ((\mathbf{X}^{(b)})^T\mathbf{X}^{(b)} + \rho\mathbf{I}_{M_b} - (\mathbf{X}^{(b)})^T(\mathbf{Z}^T\mathbf{Z})^{-1}\mathbf{H}^{(b)} - (\mathbf{H}^{(b)})^T(\mathbf{Z}^T\mathbf{Z})^{-1}(\mathbf{Z}^T\mathbf{X}^{(b)} - \mathbf{Z}^T\mathbf{Z}(\mathbf{Z}^T\mathbf{Z})^{-1}\mathbf{H}^{(b)}))^{-1},$$

For simplicity of notation let $\mathbf{J} = \mathbf{Z}^T\mathbf{Z}(\mathbf{Z}^T\mathbf{Z})^{-1}\mathbf{H}^{(b)}$. We can then simply the expression to

$$\mathbf{R}_p^{-1} = ((\mathbf{X}^{(b)})^T\mathbf{X}^{(b)} + \rho\mathbf{I}_{M_b} - (\mathbf{X}^{(b)})^T(\mathbf{Z}^T\mathbf{Z})^{-1}\mathbf{H}^{(b)} - (\mathbf{H}^{(b)})^T(\mathbf{Z}^T\mathbf{Z})^{-1}(\mathbf{Z}^T\mathbf{X}^{(b)} - \mathbf{J}))^{-1},$$

Now let

$$\mathbf{U} = \begin{bmatrix}\mathbf{H}^{(b)} & (\mathbf{X}^{(b)})^T\mathbf{Z}\end{bmatrix},$$

which is a $T \times 2C$ matrix

$$\mathbf{C} = \begin{bmatrix}\mathbf{Z}^T\mathbf{Z} & 0 \\ 0 & \mathbf{Z}^T\mathbf{Z}\end{bmatrix}^{-1},$$

which is a $2C \times 2C$ matrix

$$\mathbf{V} = \begin{bmatrix}\mathbf{Z}^T\mathbf{X}^{(b)} - \mathbf{J} \\ \mathbf{H}^{(b)}\end{bmatrix},$$

which is a $2C \times T$ matrix

$$\mathbf{R}_p^{-1} = \mathbf{S}^{-1}(([\mathbf{X}_p^{(b)})^T\mathbf{X}_p^{(b)} + \rho\mathbf{I}_{M_b}] + \mathbf{UCV})^{-1}\mathbf{S}^{-1}, \tag{6}$$

Now, using the Woodbury Matrix Identity, we can set $\mathbf{B} = \mathbf{X}_p^{(b)})^T\mathbf{X}_p^{(b)} + \rho\mathbf{I}_{M_b}$ and expand the inverse

$$\mathbf{R}_p^{-1} = \mathbf{S}^{-1}[\mathbf{B}^{-1} - \mathbf{B}^{-1}\mathbf{U}(\mathbf{C}^{-1} + \mathbf{VB}^{-1}\mathbf{U})^{-1}\mathbf{VB}^{-1}]\mathbf{S}^{-1}, \tag{7}$$

Note that $(\mathbf{C}^{-1} + \mathbf{VB}^{-1}\mathbf{U})^{-1}$ is a very small inverse matrix which is $2C \times 2C$ in size. This allows us to compute this inverse explicitly without much issue. The above expression is mathematically equivalent to $\mathbf{R}_p^{-1}$ and thus can be substituted for any instance of $\mathbf{R}_p^{-1}$ in the original ADMM algorithm. This substitution is what becomes Algorithm 3—our improved ADMM algorithm for ridge regression with covariates.

Association testing

Here we outline how association testing is performed in SafeGENIE. For each variant, we wish to calculate

$$s := \frac{\tilde{g}^T \hat{y}^*_{\text{resid,LOCO}}}{\hat{\sigma}_e \cdot \sqrt{\tilde{g}^T \tilde{g}}}.$$

Note that

$$\tilde{g} = \sigma_g^{-1} P g,$$

where $P = (I - Z(Z^T Z)^{-1} Z^T)$. Since we include a column of ones in the covariate matrix Z for mean shift correction, we do not need to apply mean correction in advance to g. Also, since the scaling factor σ_g^{-1} cancels between the denominator and the numerator, we can set it to one without affecting the result, i.e. let $\tilde{g} = Pg$. Thus, we can express the target quantity as

$$s = \frac{g^T P \hat{y}^*_{\text{resid,LOCO}}}{\hat{\sigma}_e \cdot \sqrt{g^T P g}}$$

We first directly calculate $\hat{y}^*_{\text{resid,LOCO}}$ and $\hat{\sigma}_e$. Then, we compute $g^T P \hat{y}^*_{\text{resid,LOCO}}$ by first computing

$$w := P \hat{y}^*_{\text{resid,LOCO}}$$

then computing

$$\tilde{g}^T \hat{y}^*_{\text{resid,LOCO}} = g^T w.$$

Note that w is computed once per chromosome and shared across all variants.

Next we consider $g^T P g$. We have access to a matrix R such that $RR^T = (Z^T Z)^{-1}$, using which we can express $P = I - ZRR^T Z^T$. Define

$$u := R^T Z^T g.$$

Then we can compute

$$g^T P g = g^T g - u^T u.$$

To further consolidate the computation above, we can take the following approach. We first compute

$$w := P \hat{y}^*_{\text{resid,LOCO}}.$$

Then, we take a single pass over the input genotype matrix to compute the following terms for each column g:

$$g^T g,\ Z^T g,\ w^T g.$$

Note that the first two are computed in plaintext and easily converted to secret shares, where each party sets their own share to the computed plaintext value such that the implicit sum of shares simply becomes the overall sum. The third term involves a ciphervector w and thus can be treated as ciphervector-plainmatrix multiplication.

Given these terms, we can compute u using the secret shares, then compute $g^T P g$ as well as its inverse square-root using the secret shares as well. Afterwards, we need only multiply the numerator with the inverse of the denominator (taking $\hat{\sigma}_e$ into account) and obtain the final statistics.