

1 Significance

Privacy is one of the most important topics of debate in data science that stands at the corner of many different fields, including ethics, sociology, law, political science, and forensic science. Recently, genomics has emerged as one of the major foci of studies on privacy. This can mainly be attributed to the advancement of technologies for high throughput biomedical data acquisition that bring about a surge of datasets[1, 2]. Among these, high throughput molecular phenotype datasets, like functional genomic and metabolomic measurements, substantially grow the list of the *quasi-identifiers* (such as birth date, ZIP code, gender[3]) for participating individuals, which can be used by an adversary for re-identification of the identities. With the recent announcement of Precision Medicine Initiative[4], a large body of datasets are to be generated and shared among researchers[5]. The National Institutes of Health also released the plans to encourage public access to biomedical datasets from scientific studies [5–7]. Considering the fact that one does not need many identifiers to uniquely pinpoint an individual[3, 8, 9], these datasets have the potential to exacerbate the risk of privacy breach.

Many consortia, like GTex[10], ENCODE[11], 1000 Genomes[12], and TCGA[13], are generating large amount of personalized biomedical datasets. Coupled with the generated data, sophisticated analysis methods are being developed to discover correlations between genotypes and phenotypes, some of which can contain sensitive information like disease status. Although these correlations are useful for discovering how genotypes and phenotypes interact, they could also be utilized by an adversary in a linking attack for matching the entries in genotype and phenotype datasets. For example, when a phenotype dataset is available, the adversary can utilize the genotype-phenotype correlations to statistically predict the genotypes, compare the predicted genotypes with the entries in another dataset that contains genotypes. For the entries that are correctly matching, he/she can reveal sensitive phenotypes of the individuals and characterize them. Even when the strength of each genotype-phenotype correlation is not high, the availability of a large number of genotype-phenotype correlations increases the scale of linking. In fact, an adversary can perform correct linking with relatively small number of genotypes[14, 15].

Different aspects of privacy have been intensely studied. Recently, genomic privacy is receiving much attention as a result of the deluge of personalized genomics datasets that are being generated[16, 17]. With the increase in the number of large scale genotyping and phenotyping studies, the protection of privacy of participating individuals emerged as an important issue. Homer et al[18] proposed a statistical testing procedure that enables testing whether a genotyped individual is in a pool of samples, for which only the allele frequencies are known. Im et al[19] showed that, given the genotypes of a large set of markers for an individual, an attacker can reliably predict whether the individual participated to a QTL study or not. These attacks, which we refer to as “detection of a genome in a mixture”, are one type of attacks on privacy (Fig S6). There is yet another important attack where the attacker links two or more datasets to pinpoint individuals in datasets and reveal sensitive information. One well-known and illustrative example of these “linking attacks”, although not in a genomic context, is the linking attack that matched the entries in Netflix Prize Database and the Internet Movie Database (IMDB)[20]. For research purposes, Netflix released an anonymized dataset of movie ratings of thousands of viewers, which they thought was secure as the viewers’ names were removed. However, Narayanan et al[20] used IMDB database, a seemingly unrelated and very large database of movie viewers, linked the two databases, and revealed identities and personal information (movie history and choices) of many

viewers in the Netflix database. The fact that Netflix and IMDB host millions of individuals in their databases renders the question of detection of an individual in these database irrelevant since any random individual is very likely to be in one or both of these databases but the focus of attacks turns to matching individuals in the databases. Consequently, as the databases grow, the attacks for detection of an individual in a database become unimportant and the linking attacks become more admissible in order to characterize individuals' sensitive information. In the genomic privacy context, as the size and number of the genotype and phenotype datasets increase, possibility of potentially linkable datasets will increase, which may make scenarios similar to Netflix attacks a reality in genomic privacy.

2 Innovation

There is currently a significant scarcity of tools that enable analysis and protection of genomic and phenotypic datasets. We will focus on characterizability of the individuals' sensitive information in the context of linking attacks, where the adversary exploits the genotype-phenotype correlations to link different datasets and potentially reveal sensitive information. In general, the high dimensional phenotype datasets generated in genomic studies harbor a number of phenotypes that contain sensitive information, like disease status, and other phenotypes, while not sensitive, may have subtle correlations with genomic variant genotypes. We will perform large scale analysis of the potential genotypic information leakage that different QTL datasets can cause. We will build tools that enable reporting of objective measures for genotypic information leakage from phenotype datasets. These tools will enable generating uniform and systematic analysis of privacy risks imposed by releasing new phenotype, genotype, and QTL datasets. We will also evaluate how accurately the predicted genotypes can characterize an individual. We will study the different routes for linking the phenotype and genotype datasets.

For generating a set of preliminary results that will be presented, we will use the expression quantitative trait loci (eQTL) and expression dataset s generated by the GEUVADIS project[34] and the genotype dataset from the 1000 Genomes Project. We will generalize the formalisms, however, to be applicable to any type of QTL, genotype, and phenotype datasets. We will plan to apply the developed formalisms on the datasets generated by the large scale genotyping and phenotyping projects like GTex, TCGA, HAPMAP, ICGC, ENCODE, and others.

Specifically, Many quantitative phenotypes can be linked to genotypes using public quantitative trait loci (QTL) datasets. Some of the high dimensional genomic quantitative traits and corresponding QTLs are gene expression levels (eQTLs), protein levels (pQTLs[21, 22]), DNase hypersensitivity site signals (dsQTLs[23]), ribosome occupancy (rQTLs[24]), DNA methylation levels (meQTLs[25]), histone modification levels (hiQTLs[26-28]), RNA splicing (sQTLs[29]), and also higher order traits like network modularity (modQTLs[30]). Other QTLs associated with single dimensional non-genomic phenotypes include body mass index[31], basal glucose levels[31], and serum cholesterol levels[21, 33].

3 Approach

We will address the need for new computational approaches for analyzing sensitive information leakage within 3 aims. In the first aim, we will develop statistical formalisms for quantification of the leakage of information that enables pinpointing of individuals in genotype and phenotype datasets with use of QTLs. In the second aim, we will focus on specific linking attacks and work on instantiations of the linking attacks using outliers in the phenotype datasets. In the third aim, we will focus on proposing file formats and methodologies that enable privacy preserving sharing and publishing of the phenotype datasets. Figure 1 shows how we will utilize the methodologies proposed in each aim can be combined for an integrated risk assessment for releasing QTL, phenotype, and genotype datasets.

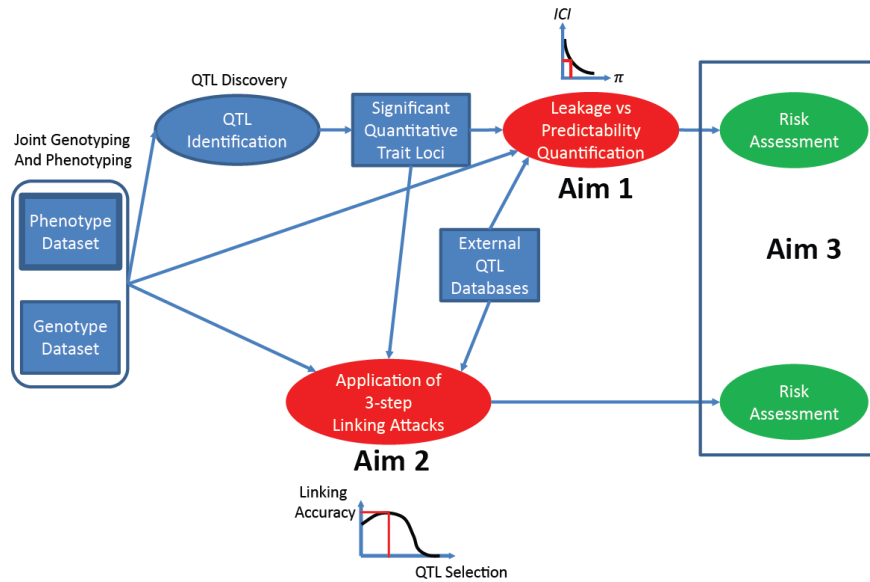


Figure 1: Generalized Risk Assessment Scenario for Genotype-Phenotype Datasets: The joint genotype and phenotype

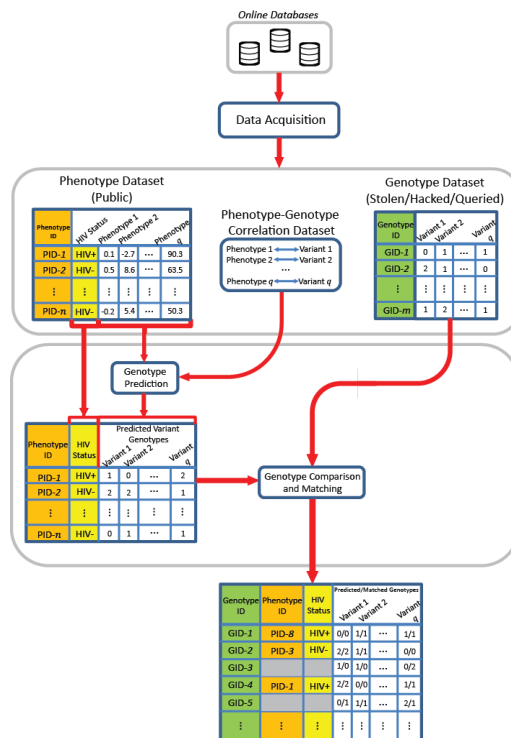


Figure 2: Schematic Representation of a Linking Attack: The attacker links the phenotype and genotype datasets using the genotype predictions. In the predictions, the attacker utilizes the QTL datasets. The resulting attack generates the linked genotype (green), phenotype (orange), and sensitive phenotype (yellow) dataset.

3.1 AIM1: Development of a Statistical Formalism for Leakage from QTL Sets

In this aim, we will develop a statistical framework for analysis and quantification of the information leakage that can be used for pinpointing and linking individuals in the phenotype and in the genotype datasets using QTL datasets.

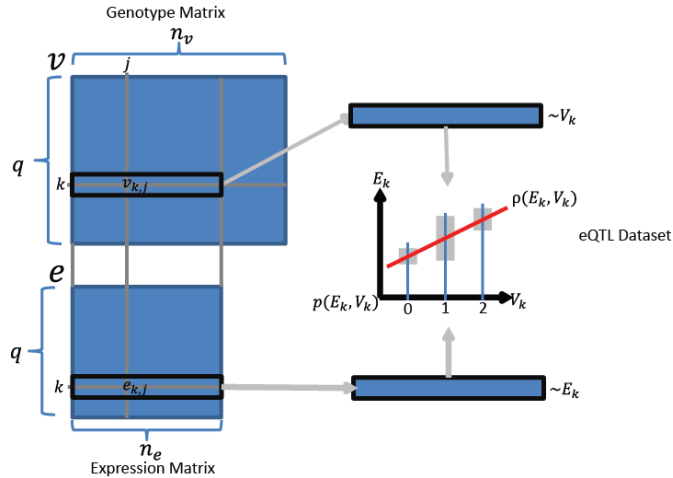


Figure 3: The representation of the genotype and expression datasets.

3.1.1 Overview of the Individual Characterization Scenario by Linking Attacks

Figure 2 illustrates the general privacy breaching scenario that is considered. There are three datasets in the context of the breach. First dataset contains the phenotype information for a set of individuals. The phenotypes can include sensitive information such as disease status in addition to several molecular phenotypes such as gene expression levels. The second dataset contains the genotypes and the identities for another set of

individuals. The third dataset contains correlations between one or more of the phenotypes in the phenotype dataset and the genotypes. In this dataset, each entry contains a phenotype, a variant, and the degree to which these values are correlated. We will focus on the gene expression datasets as the representative phenotype dataset. The abundance of gene expression-genotype correlation (eQTL) datasets makes these datasets most suitable for linking attacks.

Figure 3 illustrates the eQTL, expression, and genotype datasets. The eQTL dataset is composed of a list of gene-variant pairs such that the gene expression levels and variant genotypes are significantly correlated. We will denote the number of eQTL entries with q . The eQTL (gene) expression levels and eQTL (variant) genotypes are stored in $q \times n_e$ and $q \times n_v$ matrices e and v , respectively, where n_e and n_v denotes the number of individuals in gene expression dataset and individuals in genotype dataset. The k^{th} row of e , e_k , contains the gene expression values for k^{th} eQTL entry and $e_{k,j}$ represents the expression of the k^{th} gene for j^{th} individual. Similarly, k^{th} row of v , v_k , contains the genotypes for k^{th} eQTL variant and $v_{k,j}$ represents the genotype ($v_{k,j} \in \{0,1,2\}$) of k variant for j^{th} individual. The coding of the genotypes from homozygous or heterozygous genotype categories to the numeric values are done according to the correlation dataset. We assume that the variant genotypes and gene expression levels for the k^{th} eQTL entry are distributed randomly over the samples in accordance with random variables (RVs) which we denote with V_k and E_k , respectively. We denote the correlation between the RVs with $\rho(E_k, V_k)$. In most of the eQTL studies, the value of the correlation is reported in terms of a gradient (or the regression coefficient) in addition to the significance of association (p-value) between genotypes and expression levels. The absolute value of $\rho(E_k, V_k)$ indicates the strength of association between the eQTL genotype and the eQTL expression level. The sign of $\rho(E_k, V_k)$ represents the direction of association, i.e., which homozygous genotype corresponds to higher expression levels. This forms the basis for correct predictability of the eQTL genotypes using eQTL expression levels: The homozygous genotypes associate with the extremes of the gene expression levels and the heterozygous genotypes associate with moderate levels of expression. The eQTL studies utilize linear models to identify the gene and variant pairs whose expressions and genotypes that are significantly correlated. Given this knowledge, the adversary aims at reversing this operation so as to predict genotypes for each individual, using the respective gene expression levels and the genotype-phenotype correlation. For general applicability of the analysis, we will assume that he/she utilizes a prediction model that

estimates correctly the *a posteriori* distribution of the eQTL genotypes given the eQTL expression levels, i.e., $p(V_k|E_k)$. This will enable us to perform quantifications independent of the prediction methodology utilized by the attacker.

3.1.2 Quantification of Tradeoff between Correct Predictability of Genotypes and Leakage of Individual Characterizing Information

We will study the tradeoff the correct predictability of genotypes and the number of individuals that can be characterized with the information leakage (Figure 4). In the context of the linking attack, the attacker aims to correctly characterize n_e individuals in the expression dataset among n_v individuals in the genotype dataset. In order to correctly characterize an individual, he/she should select a set of eQTLs that he/she believes he/she can predict correctly. Next, given the individual's expression levels, the attacker should predict the genotypes for the selected eQTLs correctly such that the predicted set of genotypes are not shared by more than 1 individual, i.e., the predicted genotypes can be matched to the correct individual. In other words, the joint frequency of the set of predicted genotypes for the selected eQTLs should be $\frac{1}{n_v}$. We can rephrase this condition as following in information theoretic terms: Given the genotypes of an individual, if the attacker can correctly predict a subset of genotypes that contain at least $\log_2(n_v)$ bits of information, the individual is vulnerable to characterization of his/her phenotypes. Following this statement, we can quantify the leakage from a set of correctly predicted eQTL variant genotypes as the logarithm of their joint frequency. Assuming that the genotypes of different eQTLs are independent from each other, we can decompose the quantity of individual characterizing information that is leaked for a set of n correctly predicted eQTL genotypes:

$$ICI(\{V_1 = g_1, V_2 = g_2, \dots, V_n = g_n\}) = \sum_{k=1}^n \frac{\text{Sum individual characterizing information from all variants}}{\text{Convert the genotype frequency to number of bits that can be used to characterize individual}} \quad (1)$$

where V_k is the random variable that corresponds to the genotypes for the k^{th} eQTL, g_k is a specific genotype, and $p(V_k = g_k)$ denotes the genotype frequency of g_k within the population, and ICI denotes the total individual characterizing information. Evaluating the above formula, ICI increases as the frequency of the variant's genotype g_k decreases. In other words, the more rare genotypes contribute higher to ICI compared to the more common ones. Thus, individual linking information can be interpreted as a quantification of how rare the predicted genotypes are. The attacker aims to predict as many eQTLs as possible such that ICI for the predicted genotypes is at least $\log_2(n_v)$. ICI can also be interpreted as the number of rare SNP genotypes that an individual harbors.

In order to maximize the amount of ICI , the attacker will aim at correctly predicting as many eQTL genotypes as possible. The (correct) predictability of the eQTL genotypes from expression levels,

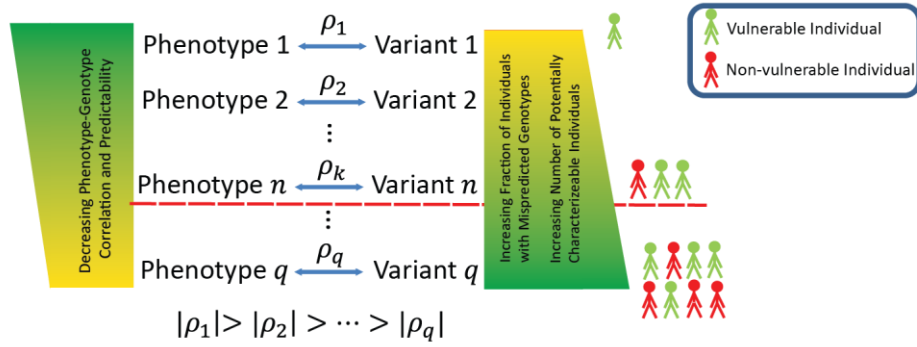


Figure 4: The tradeoff between correct predictability of the genotypes and number of individuals that can be characterized.

however, varies over the eQTL dataset as some of the eQTL genotypes are more highly correlated (i.e., more correctly predictable) with the expression levels compared to others, given in $|\rho(E_k, V_k)|$. Thus, the attacker will try to select the eQTLs whose genotypes are the most correctly predictable to maximize *ICI* leakage. Although $\rho(E_k, V_k)$ is a measure of predictability, it is computed differently in different studies. In addition, there is no easy way to combine these correlation values when we would like to estimate the joint predictability of multiple eQTL genotypes. In order to uniformly quantify the joint (correct) predictability of the eQTL genotypes using the expression levels, we use the exponential of entropy of the conditional genotype distribution given gene expression levels. Given the expression levels for j^{th} individual, we compute the predictability of the k^{th} eQTL genotypes as

$$\pi(V_k | E_k = e_{k,j}) = \frac{\text{Randomness left in } V_k \text{ given } E_k = e_{k,j}}{\text{Convert the entropy to average probability}} \exp(-1 \times \overbrace{H(V_k | E_k = e_{k,j})}^{\text{Convert the entropy to average probability}}) \quad (2)$$

where π denotes the predictability of V_k given the gene expression level $e_{k,j}$. π can be interpreted as the average probability (when sampling individuals from the population) that the attacker can correctly predict the eQTL genotype at the given expression level. In the above equation for π , the conditional entropy of the genotypes is a measure for the randomness that is left in genotype distribution when the expression level is known. In the case of high predictability, the conditional entropy is close to 0, and there is little randomness left in the genotype distribution. Taking the exponential of negative of the entropy converts the entropy to average probability of correct prediction of the genotype. In the most predictable case (conditional entropy close to 0), π is close to 1, indicating very high predictability.

As a preliminary study to show how these measures can be used jointly, we considered each eQTL and evaluated the genotype predictability versus the characterizing information leakage. We use the gene expression data from the GEUVADIS project as a representative dataset for this computation. We computed, for each eQTL, average π and average *ICI* over all the individuals (Figure 5). Most of the data points are spread along the diagonal, which indicate that there is a natural tradeoff between correct predictability and *ICI* leakage. The eQTL variants with high frequency major allele frequencies have high predictability and low *ICI* and vice versa for eQTL variants with lower major allele frequency (Fig 5, left). This is expected because the genotypes of the high frequency variants can be predicted, on average, easily (most individuals will harbor one dominant genotype) and consequently does not deliver much

characterizing information. The genotypes for the eQTLs with smaller major frequency alleles, however, are harder to predict as they are mostly uniformly distributed among population. On the other hand, these eQTLs contain high *ICI* on average. The eQTLs with high correlation (Fig 5, right) deviate from the diagonal with high *ICI* and high predictability. In principle, the adversary will aim at identifying and using these highly informative eQTLs.

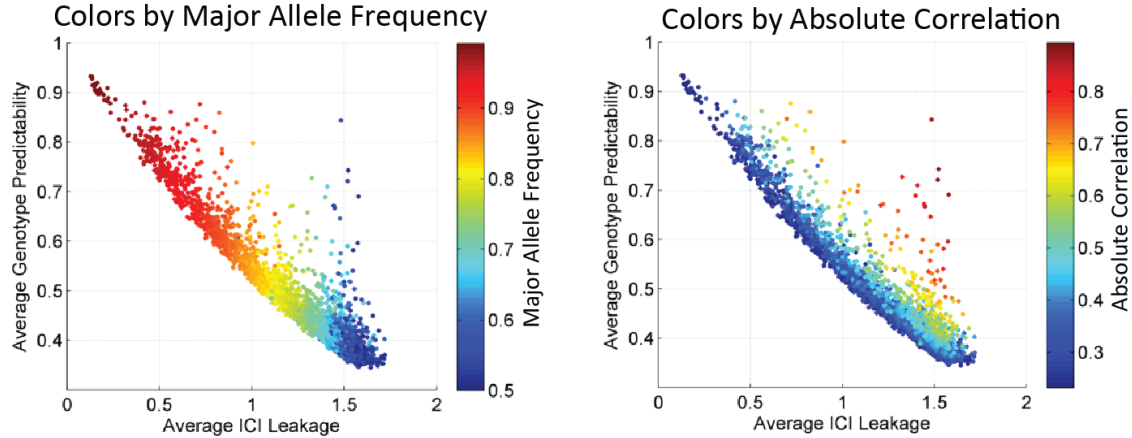


Figure 5: The scatter plot of *ICI* leakage (*x*-axis) versus the predictability (*y*-axis) of SNP genotypes. Each dot represents a SNP. SNPs are colored as per major allele frequencies (left) and per absolute eQTL correlation (right).

3.2 AIM2: Instantiating the Linking Attacks

In this aim, we will study how an attacker can instantiate linking attacks using different techniques for linking the genotype and phenotype datasets.

3.2.1 A General Framework for Analysis of Individual Characterization using Linking Attacks

We first present a tentative 3 step framework for individual characterization in the context of linking attacks. Figure 6 summarizes the steps in the individual characterization for each individual. The input is the phenotype measurements for j^{th} individual. The aim of the attacker is to correctly link the disease state of the individual to the correct identity in the genotype dataset. In the first step, the attacker selects the QTLs, which will be used in linking j^{th} individual. The selection of QTLs can be based on different criteria. As described in the previous section, the most accessible criterion is selection based on the absolute gradient or the absolute strength of association between the phenotypes and genotypes. In the case of eQTLs, this is the reported correlation coefficient, $|\rho(E_k, V_k)|$. We will study different eQTL selection criteria and how they affect the linking accuracy. The second step is genotype prediction for the selected QTLs using a prediction model. We will use different models of genotype prediction with varying complexities and study how the linking accuracy changes when different models are utilized (Figure 9). The third and final step of a linking attack is comparison of the predicted genotypes to the genotypes of the n_v individuals in genotype dataset to identify the individual that matches best to the predicted genotypes. In this step, the attacker links the predicted genotypes to the individual in the genotype dataset. We will study different linking methodologies that the adversaries can utilize.

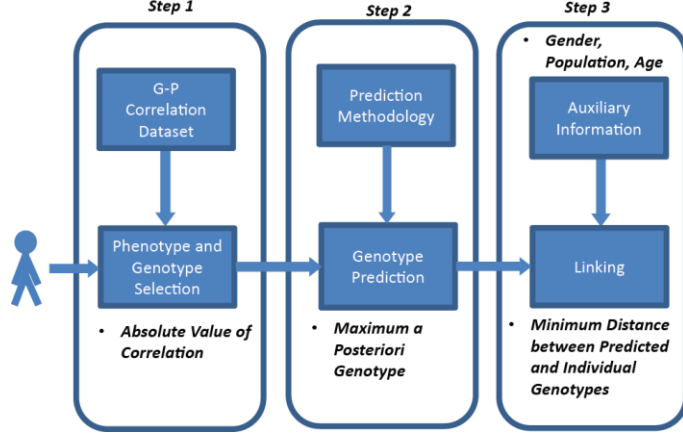


Figure 6: 3 steps of individual characterization with linking attacks.

We will study the attacker can utilize a priori knowledge about the relation between gene expression levels and genotypes and build the joint genotype-expression distributions using models with varying complexities and parameters. Even though the genotype prediction with these models may not be very accurate, the attacker can utilize a large number of eQTLs to maximize the accuracy of linking. We will first focus on highly simplified models to evaluate the risk levels associated with simple models for genotype prediction.

We will assume the attacker exploits the knowledge that the eQTL genotypes and expression levels are correlated such that the allelic effects on expression are additive and extremes of the gene expression levels (highest and smallest expression levels) are observed with extremes of the genotypes (homozygous genotypes). Therefore, given the gradient of association, the attacker can estimate coarsely the joint distribution of the genotypes and expression levels. This idea is illustrated in Fig 5a. Using an estimate of the joint distribution, the attacker can compute the *a posteriori* distribution of genotypes given gene expression levels. To quantify the extremeness of expression levels, we use a statistic we termed *extremity*. For the gene expression levels for k^{th} eQTL, e_k , *extremity* of the j^{th} individual's expression level, $e_{k,j}$, is defined as

$$extremity(e_{k,j}) = \frac{\text{rank of } e_{k,j} \text{ in } \{e_{k,1}, e_{k,2}, \dots, e_{k,n_e}\}}{n_e} - 0.5. \quad (3)$$

Extremity can be interpreted as a normalized rank, which is bounded between -0.5 and 0.5. Following from the above discussion, the adversary builds the posterior distribution for k^{th} eQTL genotypes as

$$P(V_k = 0 \mid E_k = e_{k,j}) = \begin{cases} 0 & \text{if } extremity(e_{k,j}) \times \rho(E_k, V_k) > 0 \\ 1 & \text{otherwise} \end{cases} \quad (4)$$

$$P(V_k = 2 \mid E_k = e_{k,j}) = \begin{cases} 1 & \text{if } extremity(e_{k,j}) \times \rho(E_k, V_k) > 0 \\ 0 & \text{otherwise} \end{cases} \quad (5)$$

$$P(V_k = 1 \mid E_k = e_{k,j}) = 0. \quad (6)$$

From the *a posteriori* probabilities, when the sign of the extremity and the reported correlation are the same, the attacker assigns the genotype value 2, and otherwise, genotype value 0. Finally, the genotype value 1 is never assigned in this prediction method, i.e., the *a posteriori* probability is zero. This is expected since we are focusing on the extremes and heterozygous genotype is observed at medium levels of expression. The posterior distribution of genotypes in equations (4-6) can be derived from a simplified model of the genotype-expression distribution that utilizes just one parameter.

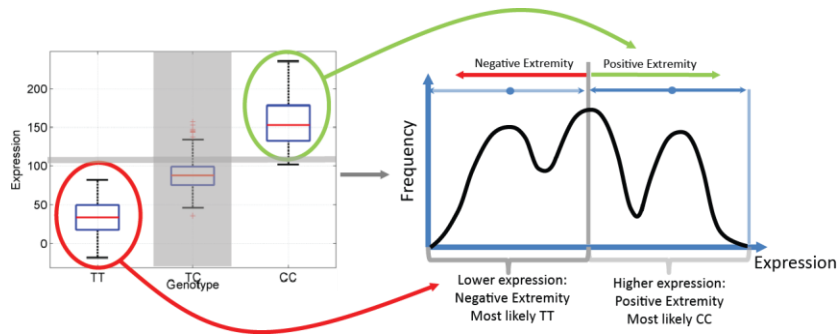
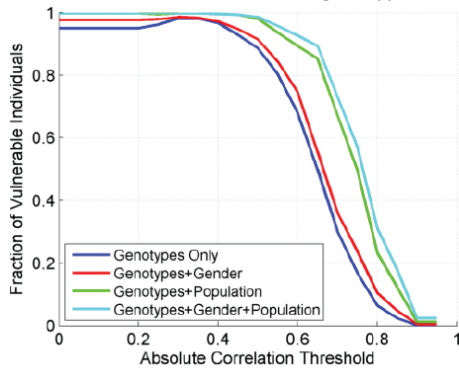


Figure 7: Extremity based genotype for an eQTL. The joint genotype versus expression distribution is shown on left. Given the distribution and the extremity, the genotypes are assigned.

As a next set of preliminary evaluation of how effective the proposed approach is, we utilized extremity based genotype prediction in the 2nd step of the individual characterization framework (Fig 7) and evaluated the fraction of characterizable individuals in the GEUVADIS dataset. We utilized the correlation based eQTL selection in step 1, then



extremity based genotype prediction in step 2. In order to demonstrate the utility of the 3-step analysis framework; we evaluated two different distance measures for linking the predicted genotypes to the individuals in genotype dataset in the 3rd step of the attack. First is based on comparison of the predicted genotypes to all the genotypes in genotype dataset. Second is based on comparison of the predicted genotypes to only the homozygous genotypes in the genotype dataset. The motivation for using this distance measure is that the extremity based genotype prediction never assigns heterozygous genotypes. Thus the heterozygous genotypes are excluded from distance computation.

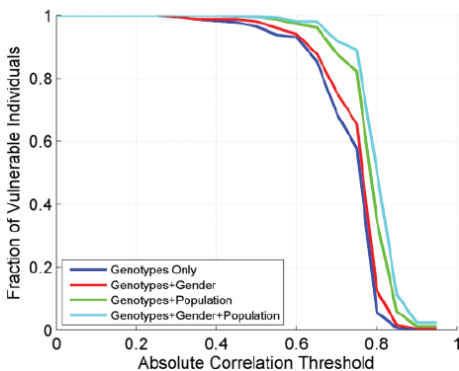


Figure 8: The accuracy of extremity based linking attack with changing eQTL selection correlation threshold.

For each measure, the attacker links the predicted genotypes to the individual whose genotypes minimize the selected distance measure. Figure 8 left and right show the fraction of vulnerable individuals for both distance measures. More than 95% of the individuals are vulnerable for most of the parameter selections for both distance measures. The homozygous genotype matching distance measure has slightly higher linking accuracy. When the gender and/or population information is present as auxiliary information (red and green plots), the fraction of vulnerable individuals increases to 100% for most of the eQTL selections.

These results show that linking attack with extremity based genotype prediction, although technically simple, can be extremely effective in characterizing individuals. We will focus on homozygous genotype matching based distance computation in the rest of the paper for simplicity of presentation.

We will extend the linking attack analysis on different QTL, phenotype, and genotype datasets.

3.3 AIM3: Building Privacy Reducing File Formats

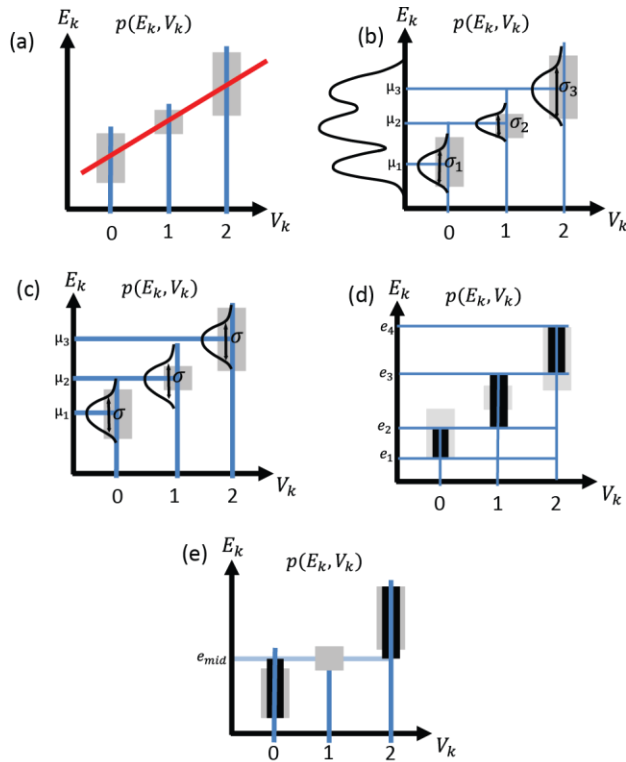


Figure 9: Different Models of Joint Genotype-Expression Distribution with changing Complexities

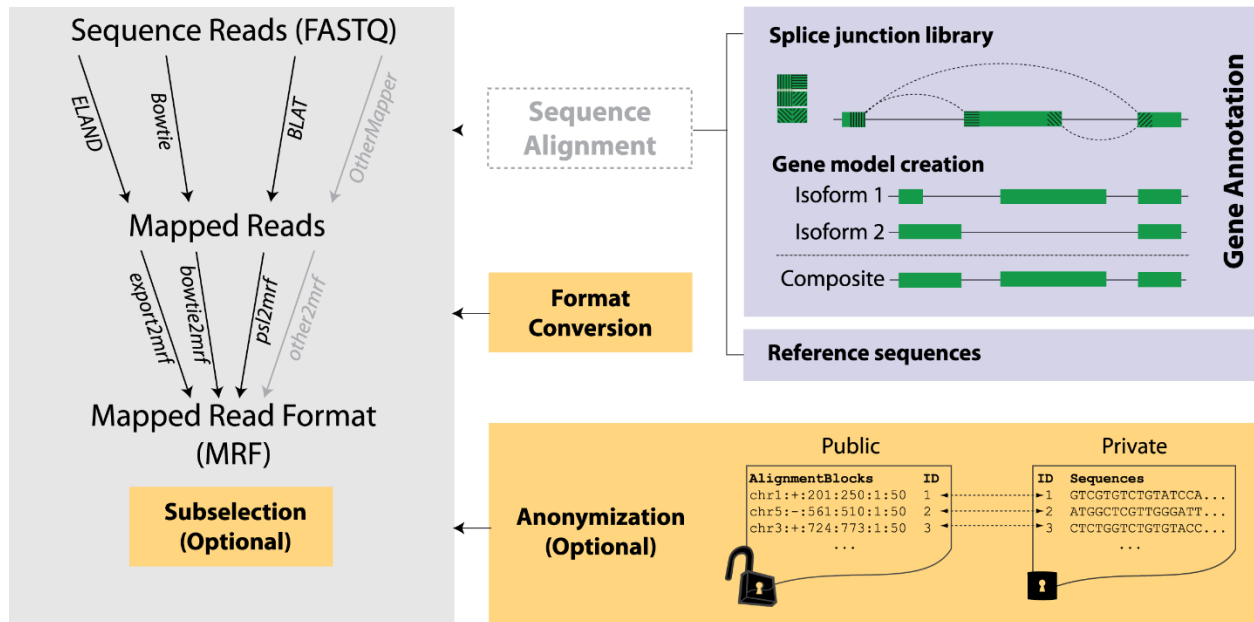


Figure 10: Anonymization Strategy for protection of RNA-seq datasets.

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