Analysis of Individual Characterizing Information Leakage in Phenotype and Genotype Datasets

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# ABSTRACT

Genomic privacy is receiving much attention with the unprecedented increase in the breadth and depth of biomedical datasets. Most studies on genomic privacy are focused on protection of variants in personal genomes. Molecular phenotype datasets, however, can also contain substantial amount of sensitive information. Although there is no explicit genotypic information in them, the subtle phenotype-genotype correlations can be used to statistically predict genotypes from phenotypes. Predicted genotypes can then be used to link the entries in phenotype datasets to those in genotype datasets. Each linkage can potentially characterize some sensitive information about an individual. This linking attack can be very accurate considering the high dimensionality of phenotypes.

In this paper, we develop a formalism for quantification and analysis of potential individual characterizing information leakage in a linking attack. We analyze the tradeoff between the predictability of the genotypes and the amount of leaked information that can be used in linking and individual characterization. Then we show how one could practically instantiate an attack focusing on the most commonly available data sets, those of RNA-seq and eQTL. We develop a three step procedure showing how an attacker would select eQTLs, statistically predict the genotypes, and then perform linking based on the predicted genotypes. The linking attack becomes particularly easy to perform when one deals with outlier gene expression levels. To study this, we developed a particular realization of this attack for the outlier cases and quantified the amount of information leakage.

# BACKGROUND

The decreasing cost of DNA sequencing [1] has rendered a massive increase in the amount of high-dimensional personalized biomedical data being generated [2]. Many consortia, like GTex [3], ENCODE [4], 1000 Genomes [5], and TCGA [6], 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 could be 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 datasets where genotypes and phenotypes are stored. For example, when phenotype dataset is available, the adversary can utilize the phenotype-genotype 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 phenotype-to-genotype correlation is not high, the availability of a large number of phenotype-genotype correlations to the adversary increases the accuracy of correct linking.

Several previous studies have demonstrated the possibility of individual identification under specific scenarios. In [7], authors propose a novel statistical analysis methodology for testing whether an individual is in a pool of samples, where only the allele frequencies are known. In [8], the authors identify the identities of several male participants of 1000 Genomes Project [5] by using the Y-chromosome short tandem repeats as an individual identifying biomarker. A more detailed review can be found [9]. In addition, different formalisms have been proposed for protecting sensitive information. For example differential privacy [10] establishes bounds on the leakage of sensitive information in statistical databases. This formalism imposes a stringent tradeoff between utility and privacy. It has been shown that differential privacy mechanisms can substantially decrease the utility of the biological information [11]. Another approach is homomorphic encryption [12], which enables performing operations on encrypted data directly. Complete protection of sensitive information is guaranteed as the data processors never interact with the unencrypted sensitive information. The drawback, however, is high computational and storage requirements. Another well-established formalism is k-anonymization [13]. The released dataset is anonymized by data perturbation techniques for ensuring that no combination of features in the dataset can be shared by less than k individuals. This approach, however, has high computational complexity and is not practical for high dimensional biomedical datasets. Several variants have been proposed that extend k-anonymity framework [14, 15]. Much of the previous literature focused on protection of genotype datasets. As the size and nature of the biomedical datasets change, it is necessary to build analysis frameworks that can uniformly quantify the predictability of genotypes and characterizability of individuals using the phenotype datasets exploiting the phenotype--genotype datasets.

In this paper, we focus on characterizability of the individuals’ sensitive information in the context of linking attacks, where the adversary exploits the phenotype--genotype correlations to reveal sensitive information. In the linking attack, there are three datasets: The first dataset contains the measurement of a series of phenotypes for a set of individuals. Examples for the phenotypes can be blood sugar level, measurement of several metabolite and biomarker levels, and gene expression levels in the blood but also disease states like HIV state, and cancer diagnosis and prognosis. As these phenotypes can be sensitive, the dataset is de-identified by removal of names and then it is released publicly. The second dataset contains the genotypes of another set of individuals. Since genotype information can reliably identify individuals as shown in previous publications, this dataset is not released publicly and released by permission only. The adversary gains access to these datasets. He then aims at characterizing the individuals in the genotype dataset by predicting the genotypes from the phenotypes and matching the predicted genotypes to the genotype dataset. For prediction, he utilizes a third dataset, where correlations between the genotypes and phenotypes are reported. For each individual in the phenotype dataset, using the value of a phenotype, the attacker computationally predicts the most likely genotype that is correlated with that phenotype. The basic idea is that the prediction will be of higher accuracy, compared to random guessing of genotypes, given that the genotype and phenotype are correlated with each other. It should also be noted that the attacker aims at predicting as many genotypes correctly as he can so that the most number of individuals are characterized correctly.

Among all the datasets, the most abundant and well-studied phenotype-to-genotype correlation dataset is expression quantitative trait loci (eQTL) datasets. These datasets are generated by genome-wide screening for correlations between the variant genotypes and gene expression levels usually through RNA sequencing or expression arrays [16–18]. The eQTL datasets are especially useful in the context of linking attacks since there is a large and growing compendium of public eQTL datasets [19]. [For example, GTex project hosts a sizeable set of eQTL dataset from multiple studies where the users can view in detail how the genotypes and expression levels are associated [3]. In order to demonstrate our results and build the formulations in a specific context, we will focus on eQTL datasets and linking of gene expression and genotype datasets. It is, however, worth noting that most of the results and analyses can be extended to other types of phenotype-to-genotype correlations.

One publication that relates to our study is [20], where the authors demonstrate that an adversary can build a model for predicting genotypes for eQTLs using gene expression levels. The authors show that given the model, individuals can be identified with high accuracy. Our study follows the study in [20] and generalizes the results of in two ways: First we study quantifying the amount of characterizing information leakage that can be generalized to other types of genotype-to-phenotype correlations. Secondly, we show that the linking can be performed in a much simplified genotype prediction approach by just utilizing the outliers in the data. For this, we introduce a new simple metric extremity and show that this metric can be utilized in genotype prediction. When large set of eQTLs are utilizes, linking can be done with high accuracy.

The paper is organized as follows: We first analyze the genotype predictability and evaluate the tradeoff between the amount of information leakage and correct predictability of the genotypes. Next we present the 3 step individual characterization framework and study different aspects of vulnerability using the framework. In the last section, to illustrate a practicality of the attack scenario, we present a simple and generally applicable genotype prediction method and evaluate the fraction of characterizable individuals on the representative dataset.

# RESULTS

## Overview of the Individual Characterization Scenario by Linking Attacks

Figure 1a 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, blood cholesterol levels, and other metabolite levels. The second dataset contains the genotypes and the identities for another set of individuals. The third dataset contains a 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. In order to formulate and demonstrate the results, we will focus on the gene expression dataset as the phenotype dataset. As explained earlier, the abundance of gene expression-genotype correlation (eQTL) datasets makes these datasets most suitable for linking attacks.

Figure 1b 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 . The eQTL (gene) expression levels and eQTL (variant) genotypes are stored in and matrices and , respectively, where and denotes the number of individuals in gene expression dataset and individuals in genotype dataset. row of , , contains the gene expression values for eQTL entry and represents the expression of the gene for individual. Similarly, row of , , contains the genotypes for eQTL variant and represents the genotype ( ϵ {0,1,2}) of variant for individual. We assume that the variant genotypes and gene expression levels for the eQTL entry are distributed randomly over the samples in accordance with random variables (RVs) which we denote with and , respectively. We denote the correlation between the RVs with . In most of the eQTL studies, the value of the correlation is reported in the eQTL dataset. The absolute value of indicates the strength of association between the eQTL genotype and the eQTL expression level. The sign of 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 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 complicated 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 given the gene expression levels. For generalization of our analysis, we assume that the he/she utilizes a prediction model that estimates the *a posteriori* distribution of the eQTL genotypes given the eQTL expression levels, i.e., . This enables us to perform the analysis independent of the prediction methodology that the attacker utilizes without making any assumptions on the prediction model that is utilized by the attacker.

## Quantification of Tradeoff between Predictability of the SNP Genotypes and Leakage of Individual Characterizing Information

We assume that the attacker will behave in a way that maximizes his/her chances of characterizing the most number of individuals. Thus, he will try and predict the genotypes for the largest set of variants that he believes are he can predict correctly. The most obvious way that the attacker does this is by first sorting the genotype-to-phenotype correlations with respect to decreasing strength of correlation. He will then predict the genotypes starting from the top genotype-phenotype pair. As he/she predicts more genotypes, he/she increases his chances of characterizing more individuals. As the attacker goes down the list, however, the correct predictability of the genotypes diminish, i.e., the strength of genotype-phenotype correlation decreases. Thus, each time he/she predicts a new genotype, he/she will encounter a tradeoff between the number of genotypes can be predicted correctly versus the cumulative correctness of the all the predicted genotypes. This tradeoff can also be viewed as the tradeoff between precision (correct predictability of the genotypes) and recall (what fraction of the individuals can be characterized by correctly predicted genotypes). In this section we will propose two measures to quantify this tradeoff.

In the context of the linking attack introduced in Section 2.1, the attacker aims to correctly characterize individuals in the expression dataset among individuals in the genotype dataset whose disease states are known. In order to correctly characterize an individual, the attacker should select a set of eQTLs that he believes he 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 frequency of the set of predicted genotypes for the selected eQTLs should be at most . 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 bits of information, the individual is vulnerable to characterization of their disease state. It should be noted that, assuming the independence of the genotypes for different eQTLs, we can decompose the quantity of individual characterizing information that is leaked for a set of correctly predicted eQTL genotypes:

where is the RV that corresponds to the genotypes for the kth eQTL, is a specific genotype (Refer to Methods Section 3.1 for more details), and denote the genotype frequency of 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 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 .

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, 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 . Thus, the attacker will try to select the eQTLs whose genotypes are the most correctly predictable to maximize *ICI* leakage. Although 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 jointly the predictability of multiple eQTL genotypes. In order to uniformly quantify the joint predictability of the eQTL genotypes using the expression levels, we use an information theoretic measure. We use the exponential of the entropy of the conditional distribution of genotype given gene expression level as a measure of predictability. Given the expression levels for individual, we compute the predictability of the eQTL genotypes as

where denotes the predictability of given the gene expression level . can be interpreted as the average probability (over sampling of individuals from the general population) that the attacker can correctly predict the eQTL genotype given the expression level. In the above equation for , the conditional entropy of the genotypes given the gene expression level 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), is close to 1, indicating very high predictability. In order to extend the predictability measure to multiple of eQTLs, we use exponential of the negative of joint conditional entropy. (Refer to Methods Section 4.1 for more details).

At this point, it is useful to note that there is a natural tradeoff between the correct predictability of eQTLs and the leaking individual identifying information. For example, the eQTLs that have the highest individual characterizing information, i.e., high , must have small genotype frequency in the population. The low frequency genotypes, however, are most likely not highly correlated with the gene expression levels, i.e., is smaller for those variants.

The relation between ICI and is important as the ICI quantifies the amount of leakage in characterizability that the predicted eQTL genotypes and quantifies how likely that characterization can occur. We will now use ICI and to evaluate how predictability changes with increasing leakage in the individual characterizing information on the GEUVADIS dataset, which we use as a representative dataset. As discussed earlier, the attacker will aim at predicting the largest number of eQTL genotypes given the expression levels to maximize his characterization power. For this, we assume the attacker will sort the eQTLs with respect to the absolute value of correlation then predict the eQTL genotypes starting from the first eQTL. In order to evaluate the tradeoff between the identifying information of the top predictable eQTLs and their predictabilities, we plotted average *ICI* versus average in Fig 2. For this, we first sorted the eQTLs with respect to the reported . Then for top *n=1,2,3,…,20* eQTLs, we estimated mean and mean *ICI* over all the samples. We then plotted mean versus mean *ICI* for each *n* which is shown in Fig 2a. There is significant leakage of *ICI* at 20% average predictability, there is approximately 7 bits of leakage and at 5% predictability, there is around 11 bits of leakage, which is enough to identify, on average, all the individuals in the sample dataset. (At 12.4% predictability, the leakage is approximately 9 bits for 6 top eQTLs.) Figure 2b and 2c also shows the average leakage for the randomized eQTL dataset where the genes and eQTLs are shuffled to generate a background model. The leakage is significantly smaller compared to the original eQTL dataset; at an average predictability of 12.4%, the average leakage is approximately 3.5 bits. On the representative dataset, these results illustrate that there is substantial amount of leakage at significant levels of predictability.

## A Generalized Framework for Analysis of Individual Characterization

In this section, we present a 3 step framework for individual characterization in the context of linking attacks. Figure 3a summarizes the steps in the individual characterization for each individual. The input is the gene expression levels for individual in the expression dataset, . 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 eQTLs (among eQTLs) that will be used in linking individual. The selection of eQTLs can be based on different criteria. As described in the previous section, the most accessible criterion is selecting the eQTLs for which absolute value of the reported correlation coefficient, , is greater than a predefined threshold. In our analysis, we evaluate the effect of changing correlation coefficient. Another criterion is to use the estimated conditional entropy of the genotype given the gene expression level, which is a measure of the predictability of the eQTL genotype. The second step is genotype prediction for the selected eQTLs using a prediction model. For general applicability of our analysis we are assuming that the attacker’s prediction model can reliably construct the posterior probability distribution of the genotypes given the gene expression levels. The attacker then uses the posterior probabilities of the genotypes to identify the maximum *a posteriori* (MAP) genotype for each eQTL. In this prediction, the attacker assigns the genotype that has the highest *a posteriori* probability given the expression level (Refer to Methods Section 4.3). The third and final step of individual characterization is comparison of the predicted genotypes to the genotypes of the 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 with the smallest number of mismatches compared to the predicted genotypes (Refer to Methods Section 4.4).

## Fraction of Individuals Vulnerable to Characterization

In this section, we utilize the general setting we presented in Section 2.3 and evaluate the fraction of characterizable individuals in the representative dataset. We assume that the attacker uses the absolute value of the reported correlation between the variant genotypes and gene expression levels to select the eQTLs. Fig SXX shows the distribution of the absolute correlation levels for the eQTL dataset. The genotypes for the selected eQTLs are predicted using MAP prediction (Refer to Methods Section 4.3). Figure 4a shows the number of selected eQTLs and the fraction correctly predicted MAP genotypes with changing absolute correlation thresholds.

Using the list of predicted eQTL genotypes selected at each absolute correlation cutoff, the attacker performs the 3rd step in the attack and links the predicted genotypes to the genotype dataset to identify individuals (Refer to Methods Section 4.4). Figure 5a shows the fraction of vulnerable individuals. The fraction of vulnerable individuals increase as the absolute correlation threshold increases and fraction is maximized at around 0.35. At this value, 95% of the individuals are vulnerable. This can be explained by the increase in characterizing information leakage as the accuracy of the predicted genotypes increase while there is a balancing decrease in the characterizing information leakage with decreasing number of eQTL genotypes predicted.

We also evaluate the scenario when the attacker gains access to auxiliary information. As the sources of auxiliary information, we use the gender and population information that is available for all the participants of 1000 Genomes Project on the project web site. We assume that the attacker either gains access to or predicts the gender and/or the population of the individuals and uses the information in the 3rd step of the attack (Refer to Methods Section 4.4). Figure 5a shows the fraction of vulnerable when the auxiliary information is available. When the auxiliary information is available, more than 95% of the individuals are vulnerable to characterization for all the eQTL selections up to when the absolute correlation threshold is 0.6. These results show that a significant fraction of individuals are vulnerable for most of the correlation thresholds that the attacker can choose.

## Individual Characterization using Extremity based Genotype Prediction

In the previous section, we presented a general framework for analysis of vulnerability. For the general applicability of the framework in different genotype prediction scenarios, we assumed that the attacker can correctly reconstruct the *a posteriori* distribution of genotypes given the gene expression levels, which is then used to estimate the MAP genotype. In general, correct reconstruction of the *a posteriori* distribution of the genotypes given expression levels may not be possible because the knowledge of only the phenotype-genotype correlation coefficient is not enough to regenerate the a-posteriori distribution of genotypes given the expression levels.

In this section, we present a simple approach for estimating the *a posteriori* distribution of eQTL genotypes given the expression levels. For this, the attacker exploits the knowledge that the eQTL genotypes and expression levels are linearly correlated with each other and therefore extremes of the gene expression levels (highest and smallest expression levels) coincide with extremes of the genotypes (homozygous genotypes). Therefore, given the gradient of association, the attacker can very roughly estimate the joint distribution of the eQTL genotypes and expression levels. This idea is illustrated Fig XX. Using 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 . For the gene expression levels for eQTL, , of the individual with expression level is defined as

Extremity is bounded between -0.5 and 0.5. Figure SXX shows the mean absolute extremity distribution of all the gene expression levels for all the individuals. The posterior distribution of eQTL genotypes can be formulated as

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. Using these probabilities, we utilized extremity based prediction and assessed the accuracy. Figure XX shows the accuracy of genotypes predictions changing correlation threshold on the selected set of eQTLs. As expected, the accuracy of genotype predictions increases with increasing correlation threshold.

We next utilized the extremity based prediction in the 2nd step of the individual characterization framework (Fig 2) 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 step 3 the individual is assigned as the individual whose genotype matches closest to the predicted genotypes. Fig XX shows the fraction of vulnerable individuals. More than 95% of the individuals are vulnerable for most of the parameter selections. In addition, 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 suggest that linking attack with extremity based genotype prediction, although technically simple, can be extremely effective in characterizing individuals.

# CONCLUSION AND DISCUSSION

In this paper we first analyzed the leakage of individual characterizing information and its predictability. We also proposed a framework for analysis of sensitive individual characterizing information leakage in the context of linking attacks. The premise of sharing genomic information is that there is always an amount of leakage in the sensitive information [21]. We believe that the quantification methodology and the analysis framework can be applied for analysis of the *ICI* leakage in the genomic datasets where the correlative relations between datasets can be exploited for performing linking attacks.

The analysis of tradeoff between predictability and leakage of *ICI* can be generalized in two ways in future studies: First, the information theoretic measures that we proposed for measuring predictability versus the *ICI* leakage can be utilized for analyzing the tradeoff in other biomedical datasets where correlations can be exploited in linking attacks. Second, the analysis that we performed can be used to extrapolate the number of vulnerable individuals in a large dataset at different predictability levels. For example, in Figure XX, at 5% predictability level there is 11 bits of *ICI* leakage, which can identify on average 2000 individuals. At 1% predictability, there is around 18 bits of *ICI*, which can identify on average approximately 64000 individuals. Depending on the probability of leakage that can be tolerated, the predictability versus *ICI* leakage can be utilized to assess whether the dataset can be released to public access or not.

We introduced a simple yet effective genotype prediction method that utilizes the simple extermity statistic. This approach capitalizes on the fact that an individual who is an outlier for a phenotype will most likely harbor a homozygous genotype.

Compared to other formalisms, our study aims more to characterize the leakage of individual characterizing information. Differential privacy, for example, aims at proposing release mechanisms for statistical databases where the mechanism guarantees that queries return results such that the probability of identifying a specific individual’s contribution to the result is vanishingly small. In order to maximize the utility of the biological data, , however, it is necessary to analyze the sources of sensitive information leakage so that one can design the utility maximizing release mechanisms [22]. Our study contributes to quantifying the individual characterizing information leakage.

# METHODS

## Quantification of Individual Identifying Information and Predictability

To quantify the individual identifying information, we use surprisal, measured in terms of self-information of the genotypes:

where is the RV that represents the k^th eQTL genotype and is a specific genotype for , is the probability (frequency) of the genotype in the sample set and denotes the individual identifying information. Assessing this relation, the genotypes that have low frequencies have high identifying information, as expected. Given multiple eQTL genotypes, assuming that they are independent, the total individual identifying information is simply summation of those:

 [[Predictability: Exponential of the conditional distribution given the gene expression levels]]

We measure the predictability of eQTL genotypes using an entropy based measure. Given the genotype RV, , and the correlated gene expression RV, ,

where denotes the predictability of given the gene expression level , and denotes the entropy of given gene expression level for . The extension to multiple eQTLs is straightforward. For the j^th individual, given the expression levels for all the eQTLs, the total predictability is computed as

***[[Cite and show that this measure is in [1/3,1] for one genotype. The interpretation of this measure is that the prediction process is converted to random guessing with uniform probability distribution where average correct prediction probability is \pi. This is the reciprocal of Shannon diversity; the average number of genotype predictions that you can randomly equally likely choose from.]]***

In addition, this measure is guaranteed to be between 0 and 1 such that 0 represents no predictability and 1 representing perfect predictability. The measure can be thought as mapping the prediction process to a uniform random guessing where the average correct prediction probability is measured by .

## Estimation of Genotype Entropy for Quantification of Predictability

[[How did we estimate the genotype entropy and conditional specific entropies?]]

[[We bin the expression values to log\_2(N\_i) different bins \cite{…}]]

## MAP (Maximum *a-posteriori*) Genotype Prediction

[[Describe the binning and MAP selection of genotypes]]

[[Must include SNP selection such that some of the genotypes are not assigned any genotype bc of the selection]]

## Linking of the Predicted Genotypes to Genotype Dataset

Given a set of predicted eQTL genotypes for individual , , the attacker links the predicted genotypes to the individual whose genotypes have the smallest distance to the predicted genotypes:

 denotes the index for the linked individual and represents the distance between the predicted eQTL genotypes and the genotypes of the a^th individual:

where is the match indicator:

Finally, individual is vulnerable if . When auxiliary information is available, the attacker constrains the set of individuals while computing to the individuals with matching auxiliary information. For example, if the gender of the individual is known, the attacker excludes the individuals whose gender does not match while computing . This way the auxiliary information decreases the search space of the attacker.

## Extremity Attack

[[Define the extremity attack: Correlation and extremity parameters]]

# DATASETS

[[GEUVADIS dataset, and eQTLs; 1000 genomes dataset]]

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