

Information theory based measures for quantification of
private information leakage and privacy-preserving file
formats for functional genomic experiments

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Abstract

Functional genomics experiments provide a wealth of insight on genomic activities (i.e. gene expression or transcription factor binding) related to developmental stages or diseases that are essential for personalized medicine. Although these activities are not necessarily tied to an individual's genotype, quantification of such activities is only possible using sequencing data that involves individual's genotypes. Here we focus on the quantity of sensitive information in functional genomic experiments such as ChIP-Seq, RNA-Seq and Hi-C, as majority of these data are considered to be safe to share due to inadequate sequencing depth and incompleteness. We derive novel information theory based measures and apply these measures to quantify the amount of leaked information in 24 functional genomic assays from ENCODE at varying coverages. We show that individuals are vulnerable to identification even when small amounts of sequencing data are available to adversaries. We also show that with summation of functional genomics experiments and imputation through linkage disequilibrium, the leaked number of variants can reach the total number of variants in an individual's genome. We then provide a theoretical framework where the amount of leaked information can be predicted from depth and breadth of the coverage as well as the bias of experiments. Based on our findings, we propose privacy enhancing file formats with minimal loss of utility. Presented frameworks here can be used for quantification of private information from large functional genomics datasets before their release and conversion of sensitive data to private formats.

1 Introduction

With the decreasing cost of DNA sequencing technologies, the number and the size of the available genomic data have exponentially increased and become available to a wider group of audiences such as hospitals, research institutions and individuals [1]. In turn, privacy of individuals has become an important aspect of biomedical data science [2, 3] as availability of genetic information gives rise to privacy concerns such that genetic predisposition to diseases may bias insurance companies [?] or create unlawful discrimination by employers.

Early genomic privacy studies focused on identification of individuals in a mixture by using phenotype-genotype association [5, 6]. These revealed that private information about an individual such as participation to a drug-abuse study [5, 6] can be revealed. With the increase of large-scale genomic projects such as Personal Genome Project (PGP) [7] or recreational/commercial genomic databases, researchers showed that multiple datasets can be linked together to infer sensitive information such as participant's surnames [8] or addresses [9]. Such cross-referencing relies on quasi-identifiers, which are pieces of information that are not unique identifiers by themselves, but are well correlated with entities that might be unique identifiers or can be unique identifiers when combined with other quasi-identifiers and become personally identifying information [10].

Functional genomics experiments provide a wealth of information on genomic activities related to developmental stages or diseases that are essential for personalized medicine. These are large-scale, high-throughput assays to quantify transcription (RNA-Seq) [11], epigenetic regulation (ChIP-Seq) [12] or 3D organization of genome (Hi-C) [13] in a genome-wide fashion under different conditions (e.g. samples from patients and healthy individuals). In turn, these experiments produce sequencing data that involve individual's genotypes. Phenotypical information such as gene expression levels or signal tracks are shown to be important quasi-identifiers that can be used to identify individuals as they are likely correlated with genotypical information [14, 15, ?].

Therefore, the privacy studies based on functional genomics data focused on identification of individuals through phenotypical data that is publicly available. This is partly due to the sequencing data of these experiments that require high genome coverage such as Hi-C or RNA-Seq often require special permission for access as raw reads contain a significant amount of sensitive genetic information. The raw reads can be used to identify the private SNPs, small indels, and structural variants. Nonetheless, sequencing data of functional genomics experiments that does not require substantial depth are sometimes considered to be safe to share without privacy concerns as the nature of these data is biased and partial. A good example is that the genome of HeLa cell line requires special access, while we can access the DNA reads from ChIP-Seq data [17].

On the flip side of the coin is the utility of these sequencing data. Open data helps the advancement of biomedical data science not only with the easy access to the data, but also helping with the speedy assessment of tools and methods and in turn reproducibility. Funding agencies and research organizations are increasingly supporting new means of data sharing and new requirements for making data publicly available. Embracing the both side of the coin, we ask the questions of how much information is enough information to identify individuals and how we can protect the sensitive information with minimum loss of utility in a publicly data sharing mode. To this end, we derive novel information theory based measures and apply these measures to quantify the amount of leaked information in 24 functional genomic assays from ENCODE [18] at varying coverages. Furthermore, we develop new file formats that allow the public sharing of read alignments of functional genomics experiments while protecting the sensitive information.

In this study, we use NA12878 as a case example and her 1000 genomes [20] genotypes as gold standard genotypes. We sample reads from the sequencing data of functional genomics experiments at increasing coverages and detect SNVs and indels using Genome Analysis Toolkit (GATK) best practices recommendations [21, 22]. We propose a new metric for quantifying the amount of

information that can be obtained from sequencing data with respect to the gold standard. We next present a simple and practical instantiation of a linking attack with the assumption of adversaries accessing only a portion of the sequencing data. We show that individuals are vulnerable to identifications even at small coverages of sequencing data. We further show that with summation of functional genomics experiments and imputation through linkage disequilibrium, the leaked number of variants can reach the total number of variants in an individual's genome. We then provide a theoretical framework where the amount of leaked information can be predicted from depth and breadth of the coverage as well as the bias of the experiments. Finally, we focus on ways to publicly share alignment data without compromising individual's sensitive information. We propose privacy enhancing file formats that hide variant information, are compressed and have minimum amount of utility loss.

2 Results

2.1 Information Theory measures to quantify private information in an individual's genome

An individual's genome can be represented as a set of variants. Each variant is composed of the chromosome it belongs to, location on that chromosome, the alternative allele and its corresponding genotype. Let $S = \{s_1, s_2, \dots, s_i, \dots, s_N\}$ be the set of variants, then each variant can be represented as $s_i = \{v_i, g_i\}$, where v_i consists of the location and alternative allele information and g_i denotes the genotype of the variant as 1 for heterozygous variant and 2 for homozygous variant. We can then calculate the self-information of S in bits as

$$h(S) = - \sum_{i=1}^{i=N} \log_2(p(s_i)). \quad (1)$$

In eq.1 N is the total number of variants in an individual's genome, $p(s_i) = n_i/n_T$, where n_i is the number of individuals with variant s_i and n_T is the total number of individuals in the panel. Note that $h(S)$ is an estimate of the real information in a situation where the population that the individual belongs to is not known and the number of individuals are finite. Eq.1 holds only if variants are independent of each other, which is not the case due to the correlation between variants in linkage disequilibrium (LD). In theory, the population that the individual belongs to can easily be predicted by using a few variants. However, from an adversary's perspective, this will add one more layer of calculation, i.e computational and time cost to identification attack. Eq.1 also cannot be equal to the information when we consider all the individuals in the world ($n_t \rightarrow \infty$). Therefore from hereof we will refer Eq.1 as the naive information.

To be able to understand whether naive information is a good estimate, we first calculate the information with the consideration of LD scores taken from the European population of HapMap project [23]. LD scores are pairwise correlations between variants, which we consider as the prior information on the existence of a variant given other variants in the same LD block exist in a genome. Then the information with LD consideration is calculated as

$$h^{LD}(S) = - \sum_{i=1}^{i=N} (1 - mLD(s_i, s_j)) h(s_i) \quad (2)$$

$LD(s_i, s_j)$ is the maximum LD correlation of variant s_i such that $mLD(s_i, s_j) = \max_{i \neq j, j \in (1, \dots, N)} LD(s_i, s_j)$, where $mLD(s_i, s_j) \neq mLD(s_j, s_i)$.

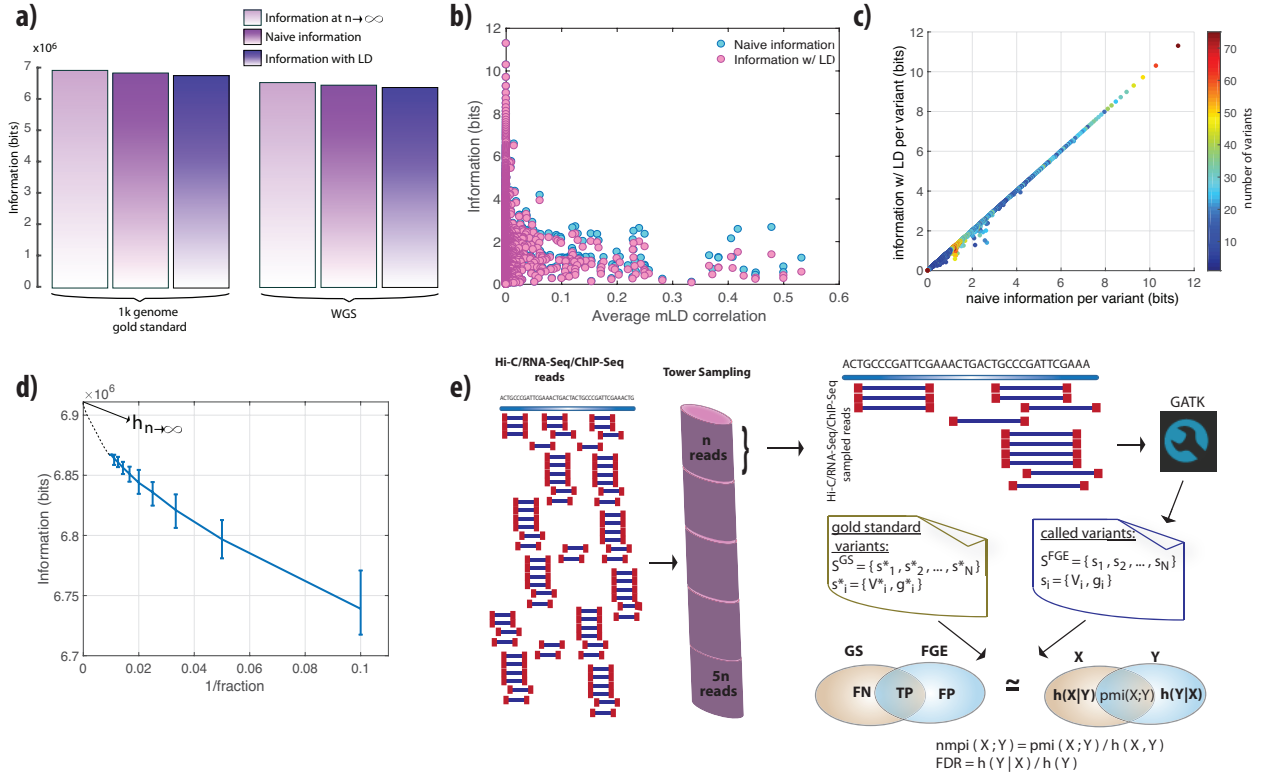


Figure 1: Comparison of naive information measure with information with LD consideration and sample size correction. (a) Difference between the naive information, information with LD consideration and extrapolated information when population size is infinite. (b) The maximum LD score for each variant are averaged over per information and plotted against information. Highly informative variants do not exhibit difference when information is calculated sing naive approach vs. with LD consideration. (c) Naive information vs. information with LD consideration per each variant in an LD block. Only low information variants show slight difference between two approaches. (d) Naive information vs. inverse fraction of the data sampled from the 1000 genomes population. y -intercept is extrapolated from the fitted curve and denotes the information when the population size is infinite. Error bars are calculated using $100\times$ bootstrapping. (e) The process of sampling reads from functional genomics experiments for the calculation of pointwisw mutual information between 1000 genomes gold standard variants for NA12878 in different coverages.

Figure 1a shows a negligible difference between the naive information and information with LD consideration for NA12878 genome. To understand the lack of difference better, we calculate the self-information of each variant in an LD block with and without LD consideration. We show that highly informative variants do not exhibit any difference due to the low LD correlations (Fig-

ure 1b). We further show that the number of variants that have difference between information with and without LD consideration is small compared to highly informative variants having low LD correlations on average.

We then estimate the information when the population size is infinite [24]. We sample fractions individuals from the 1000 genomes phase I panel (total of 2504 individuals) and calculate the information using the sampled distribution of genotypes. We repeat this calculation for 100 times and calculate the mean information for each sampled fraction. We found a power relationship with two terms ($y = ax^b + c$) between the inverse sampled fraction and the information ($R = 0.99$). The y-intercept (c) of the curve is the extrapolation of information when the population size goes to infinity ($1/\infty = 0$, Figure 1c). We again found a negligible difference between the naive information and the information when the population size is infinite (Figure 1a). The information is also calculated by starting from a single individual and adding individuals one by one to the population (SI Figure 1a). These individuals are simulated using the genotype frequencies in the 1000 genomes panel and the LD information from HapMap project (see SI methods). Both the information calculation and the KL -divergence between different size populations show that as the size of the population increases, the difference in the information decreases and eventually becomes negligible (SI Figure 1a-b)

In summary, calculations above show that the naive information can be an accurate approximate to the private information content of an individual's genome when the individual's population is not known and the population size is bound by the number of individuals in 1000 genomes panel due to the relationship of information at $n \rightarrow \infty \geq \text{naive information} \geq \text{information with LD}$ (Figure 1a). That is, an adversary with no prior knowledge on the population of the sample and limited number of individuals in a known genotype panel can accurately approximate the private information in the sample.

2.2 Information Theory measures to quantify private information leakage in a functional genomics experiment

In an effort to understand the relationship between the leaked information and the coverage as well as for a fair comparison, k amount of reads were sampled from the 24 different functional genomic experiments and from WGS and WES data of NA1278 (see SI Table 1). Genome Analysis Tool Kit (GATK) is used to call SNVs and indels with the parameters and filtering suggested in GATK best practices. The genotypes in 1000 genomes panel for NA1278 is used as the gold standard. We use pointwise mutual information (pmi) as a measure to quantify the association between the gold standard and the called variants. If $S^{GS} = \{s_1^*, \dots, s_i^*, \dots, s_M^*\}$ is the set of variants from the gold standard and $S_k^{FGE} = \{s_1, \dots, s_i, \dots, s_M\}$ is the set of variants called from the k reads of a functional genomics experiment, then the set $A = S^{GS} \cap S_k^{FGE}$ contains the variants that are called and are in the gold standard set. If $A = \{a_1, \dots, a_i, \dots, a_T\}$, then

$$pmi(GS; FGE^k) = - \sum_{i=1}^{i=T} \log_2(p(a_i)) \quad (3)$$

We then add k more reads to the sampled reads and repeat the calculation. This procedure is repeated till we deplete all the reads of a functional genomics experiment. Overall process is depicted in Figure 1e.

2.3 Private information leakage in 24 functional genomics experiment at different coverages

The pmi values for 24 functional genomics experiments are calculated at different coverages. These experiments involve whole genome approaches such as Hi-C, transcriptome-wide assays such as RNA-Seq and targeted assays such as ChIP-Seq of histone modifications and transcription factor binding. In addition, the pmi is also calculated for WGS, WES, and SNP-ChIP for compar-

ison (Figure 2).

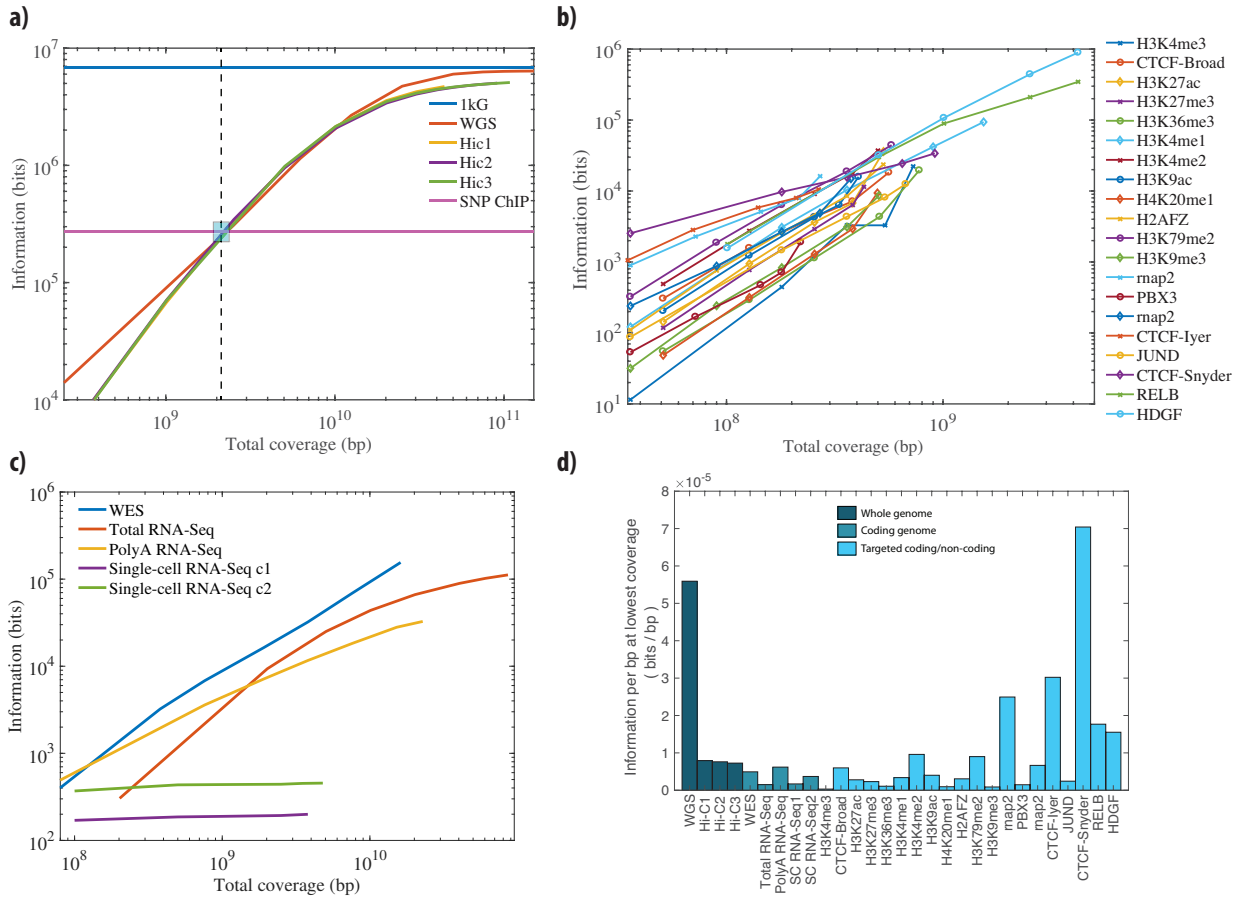


Figure 2: The pointwise mutual information calculated for 24 different functional genomics assays and WGS, WES and SNP ChIP data using NA12878 1000 genomes variants as gold standard. (a) The pmi values for WGS and three different primary Hi-C experiments plotted at different coverages. The information contents of the gold standard (1kG in blue) and SNP ChIP (in pink) are added for comparison. (b) The pmi values for 20 different ChIP-Seq experiments targeting histone modifications and transcription factor binding plotted at different coverages. (c) The pmi values for WES, total RNA-Seq, polyA RNA-Seq and single-cell RNA-Seq from two different cells plotted at different assays. (d) The pmi values per basepair plotted using the lowest total coverage for all the assays.

As expected Hi-C data contains almost as much information as WGS and more information than SNP ChIP arrays. In the beginning of the sampling process, WGS data contains more information than Hi-C. As we sample nucleotides that are between around 1.1 and 10 billion bps, the information content of Hi-C surpasses the WGS data (Figure 2a). We speculate that this is due to better

genotyping quality of the genomics regions that are in spatial proximity, as Hi-C has a bias of sequencing more reads from those regions. As expected, we cannot infer as much information from ChIP-Seq reads (Figure 2b). However, surprisingly many of the ChIP-Seq assays such as the ones targeting CTCF and RNAPII contain a great amount of information at low coverages. Furthermore, comparison between WES and different RNA-Seq experiments show that none of the RNA-Seq experiments contain as much information as WES, which is due to the fact that RNA-Seq captures reads only from expressed genes in a given cell (Figure 2c). The unexpected observation is that more information can be inferred from polyA RNA-Seq data at low coverages compared to WES and total RNA-Seq. To be able to make a fair comparison between all these assays, we calculate the pointwise mutual information per bp at the lowest coverages depicted in Figure 2a–c ($\text{pmi}(\text{FGE};\text{GS})/\text{total coverage}$). We found that ChIP-Seq reads targeting CTCF contains even more information per basepair than WGS data at the lowest coverage we sample (Figure 2d).

2.4 Genotyping accuracy

In light of the above findings, in which genotyping can be done using low depth, biased functional genomics experiments, we assess the accuracy of genotyping by calculating the false discovery rate at different coverages. This also measures how much noise that each assay captures. The false discovery rate is defined as the ratio between the information obtained from the incorrectly called variants ($h(\text{FGE}—\text{GS})$) and the information obtained from all the called variants ($h(\text{S})$), namely

$$FDR(\text{FGE}^k) = \text{pmi}(\text{FGE}^k; \text{GS}) / h(\text{S}^{\text{FGE}}) \quad (4)$$

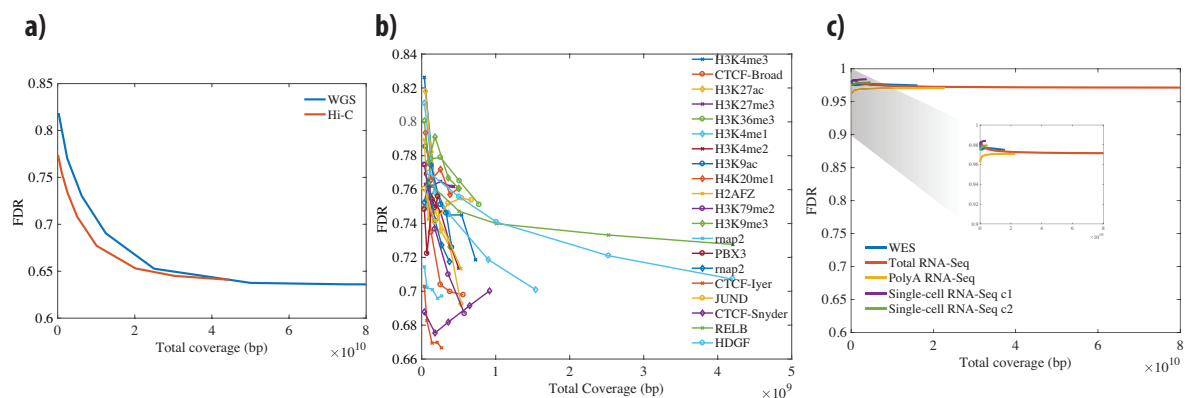


Figure 3: **False discovery rate of functional genomics experiments at different coverages (a)** FDR comparison for Hi-C and WGS data at different sampled coverages. **(b)** FDR comparison for different ChIP-Seq experiments at different coverages. **(c)** FDR comparison for WES and different RNA-Seq experiments.

Figure 3a shows that the false discovery rate for Hi-C data is lower compared to WGS data at lower coverages. We attribute it to the deeper sequencing of the genomics regions in close spatial proximity. Hence, sampling more reads from those regions at low coverages is more likely compared to uniform sampling of reads from WGS. ChIP-Seq data has comparable false discovery rate to WGS and Hi-C data, ChIP-Seq targeting CTCF having the lowest FDR (Figure 3b). We further find that assays targeting transcriptome such as WES and RNA-Seq produce the noisest genotypes among all the assays, only around 10% of the called variants being the correctly called variants (Figure 3c).

2.5 Linking attack scenario

Linking attacks aim at re-identification of an individual by cross-referencing datasets (Figure 4a). For example, in an hypothetical scenario, the attacker aims at querying an individual's HIV status from his/her phenotype data available through functional genomics experiments. Majority of linking attacks to this date focused on phenotypes, which the attacker finds the relationship between the phenotype and genotype data and use this relationship to link the HIV status to

the genotype data set. However, in this study, we go one step back from the phenotype data and directly inferred genotypes from the read files associated with the phenotype as, for example, majority of fastq and bam files of ChIP-Seq experiments are publicly available. For this, the attacker calls variants directly from the reads of anonymized functional genomic experiments. Then he/she compares the called noisy and incomplete genotypes to the genotype data panel and finds the entry that have the highest pointwise mutual information. This reveals the sensitive information for the linked individual to the attacker. We also consider a scenario that the attacker has access increasing amount of reads in situations such as the attacker can query the sequencing data from a consortium certain amount at a time or has limited computing power.

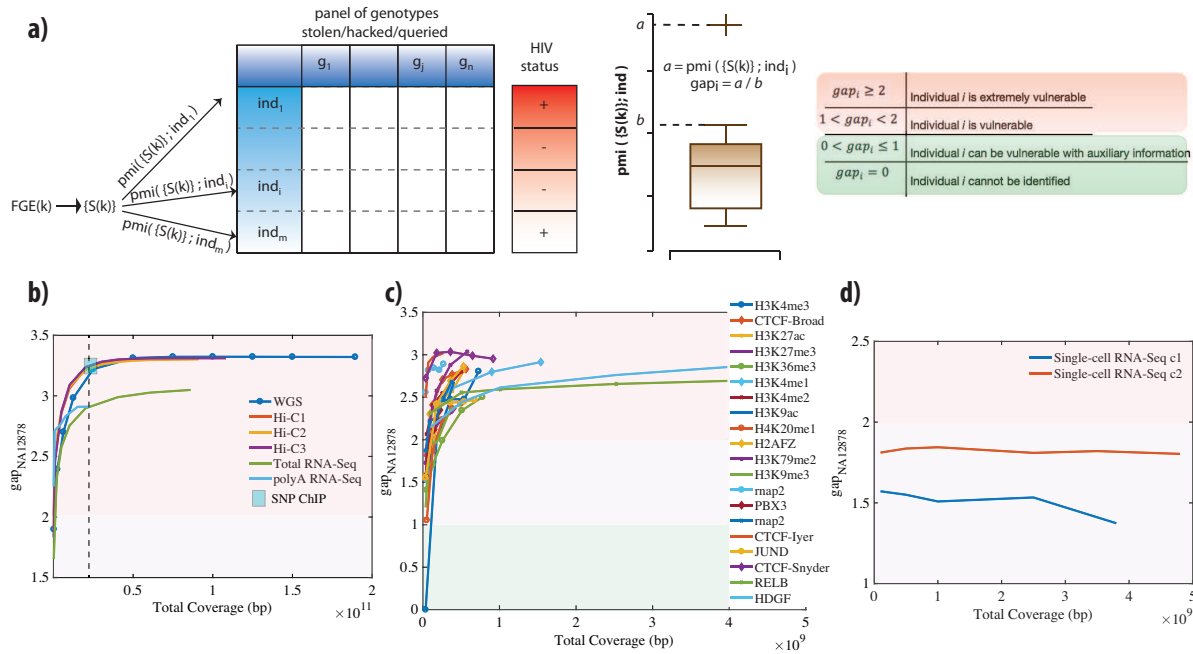


Figure 4: **Illustration of a linking attack and the accuracy of linking.** (a) The publicly available anonymized reads from functional genomics experiments contains a set of variants and HIV status for the sample that the functional genomics experiment was performed at increasing coverages. The panel of genotypes contains the variants and associated genotypes for m individuals. The attacker links the inferred variants and genotypes to the panel of genotypes by using the best matched pointwise mutual information. The linking potentially reveals the HIV status for the linked individual. (b) Comparison of gap for NA12878 at different coverages for Hi-C and Total/PolyA RNA-Seq reads. WGS and SNP-ChIP are also added for comparison. (c) Comparison of gap for NA12878 at different coverages for 20 different ChIP-Seq experiments. (d) Comparison of gap for NA12878 at different coverages for single-cell RNA-Seq experiments.

Based on the pmi values of each experiment at different coverages, we define a metric for linking accuracy called gap_i . To calculate this metric, we first rank all the $pmi(S_k^{FGE}; individual_i)$ where S_k^{FGE} is the set of called genotypes from the functional genomics experiment at total coverage k and $individual_i$ is the set of genotypes of individual i in the panel of genotypes. gap_i for each individual i at total coverage k is calculated as;

$$gap_i = \begin{cases} \frac{pmi(S_k^{FGE}; individual_i)}{pmi(S_k^{FGE}; individual_j)}, & \text{if } rank(pmi(S_k^{FGE}; individual_i)) \leq 5 \text{ and } rank(pmi(S_k^{FGE}; individual_j)) = 2 \\ 0, & \text{otherwise} \end{cases}$$

We then define that if gap_i is 0 for the individual i , whose functional genomics data is used, then the individual cannot be identified as there are other individuals in the panel that have the matching genotypes. If $0 < gap_i \leq 1$, then the individual i might be vulnerable with auxiliary data such as gender or ethnicity, because he/she is in the top 5 matching individuals. If $1 < gap_i \leq 2$, then the individual i is vulnerable as we can identify him/her with 1 to 2 fold difference between him/her and the second best match. Lastly, if $gap_i > 2$, then the individual is extremely vulnerable with more than 2 fold difference between him/her and the second best match (Figure 4a).

We find that NA12878 is extremely vulnerable even at the lowest sampled coverages for Hi-C and RNA-Seq data (Figure 4b). More interestingly between around 1.1 and 10 billion basepairs, the Hi-C data exhibits higher linking accuracy than WGS data, consistent with the previous observation of pmi shown in Figure 2a. The total of coverage of ChIP-Seq data compared to Hi-C and RNA-Seq is quite low (SI Table I). However, the linking accuracy of ChIP-Seq is as good as Hi-C and WGS (Figure 4b), which shows extreme vulnerability of individuals with respect to release of such small amount of data. More strikingly, attacker can link NA12878 by using the reads of single-cell RNA-Seq data, which has small coverages with high accuracy (Figure 4d).

2.6 Individual's genome can be accurately approximated from publicly available data by imputation - should I not make this a separate section?

To answer the question whether an attacker can correctly assemble an individual's variants by only using the reads from ChIP-Seq and RNA-Seq experiments, we impute variants by using IMPUTE2 [25, 26, ?] using the variants called from ChIP-Seq and RNA-Seq experiments. We then collected all the called and imputed variants in a set. Although imputed variants do not contribute to the information due to high correlation with the called variants (SI Figure 2), total number of captured variants increases significantly (Figure 5a). By using shallow sequencing data of ChIP-Seq and RNA-Seq, we were able to call and impute variants almost as many as the gold standard variants.

We then ask the question if we can infer potentially sensitive phenotypes from these variants. Figure 5b shows a small set of example variants associated with physical traits such as eye color, hair color or freckles. Many of these variants are in the called set of Hi-C, ChIP-Seq and RNA-Seq data. Number of variants associated with traits further increases with imputation as expected.

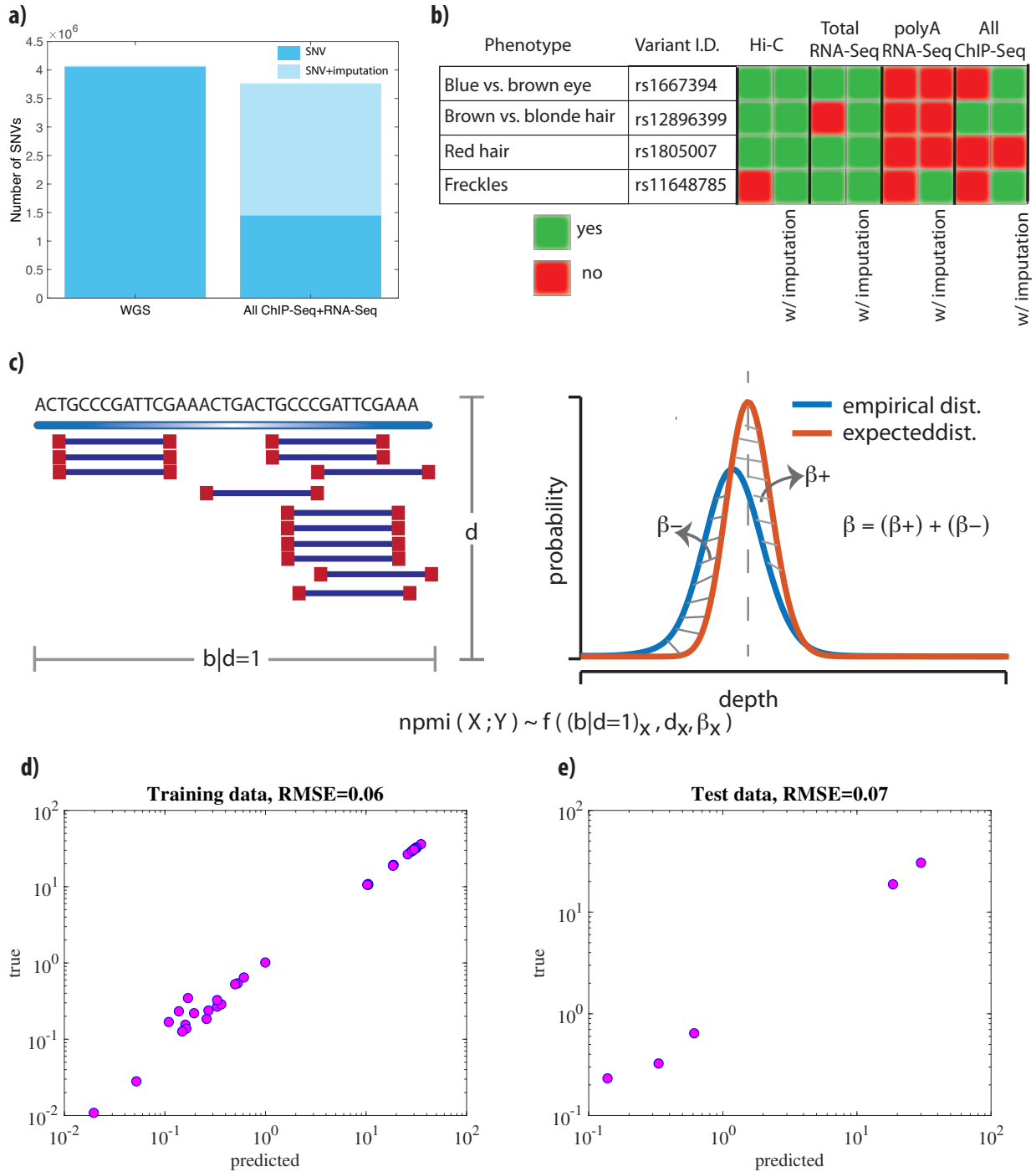


Figure 5: Individual's genome can be approximated and sensitive phenotypes can be inferred from publicly available data by imputation and a theoretical framework for prediction of amount of leaked data (a) Number SNVs called from WGS data and all of the ChIP-Seq and RNA-Seq data together with and without imputation. (b) Variants associated with physical traits and if they present in the called variants from different functional genomics experiments before and after imputation. (c) Features of the theoretical framework - write more. (d) Accuracy of fitted model on training set- write more (e) Accuracy of fitted model on test set - write more

2.7 Toy model for prediction of amount of leaked data without variant calling

Explain Figure 5 c, d and e.

2.8 Unique combination of common variants contribute significantly to the information leakage and linking accuracy

- Inspired from differential privacy, we did Figure 6a - Iteratively removed rare variants and calculated information and linking accuracy (Figure 6b) - We can still link the individual

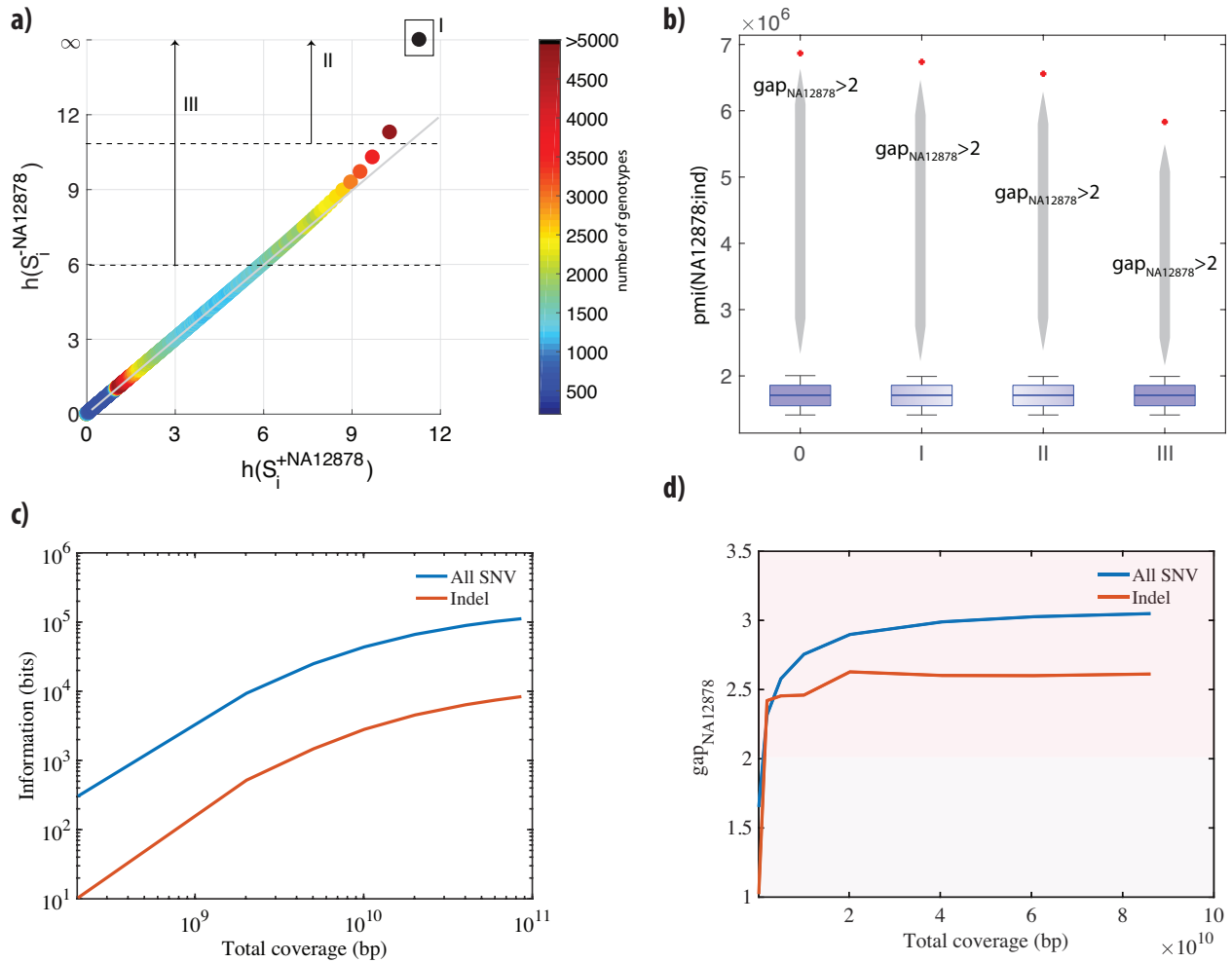


Figure 6: **to discuss** (a) Information of the variant before and after addition of NA12878 to the population. We iteratively removed variants from the set as (I) only the variants that is only NA12878 specific, (II) the variants that have an information of 11 or higher bits after removal of NA12878 from the population, (III) the variants that have an information of 6 or higher bits after removal of NA12878 (b) Linking accuracy for every iteration of removal of NA12878 variants from the set. (c) Information of all the variants that are called from Total RNA-Seq reads vs. the information of the indels that are called from Total RNA-Seq reads. (d) Linking accuracy when we consider all the variants that are called from Total RNA-Seq reads vs. the linking accuracy when we consider only indels called from Total RNA-Seq reads.

2.9 Privacy-enhancing file formats for functional genomics experiments

- Indels can be inferred from the current MRF - Refer to Figure 6c and 6d for the possibility of linking with using only indels of the noisiest data set we have - total rna-seq - Describe the new

MRF (Figure 7)

	BAM Code	MRF representation
(1) Perfectly mapping reads		
	xM x: read length	Chr n : strand : Start : End : x
(2) Reads map to splice junctions		
	$yMzNtM$ z: length of junction	Chr n : strand : Start1 : End1 : y , Chr n : strand : Start2 : End2 : z
(3) Split read with insertion		
	$yMzItM$ z: length of insertion	Chr n : strand : Start1 : End2 : y+t
(4) Split read with deletion		
	$yMzDtM$ z: length of deletion	Chr n : strand : Start1 : End2 : y+t
(5) Split read with soft clipping		
	$aSxMbS$ a+x+b: read length	Chr n : strand : Start1 : End1 : x
(6) Split read with hard clipping		
	$aHxMbH$ a+x+b: read length	Chr n : strand : Start1 : End1 : x

Figure 7: MRF: to discuss

3 Discussion

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