Supplementary Material for
Biological Replication in ChIP-Seq Experiments

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S-1 Simulation assessing assumptions for independent filtering of low read count windows

During preprocessing steps (described in Section 3.1 of the main text), BinQuasi filters out genomic windows with few reads across all replicates (by default, less than 20). Bourgon et al. (2010) [11] show that use of a filtering criterion that is independent of the test statistic under the null hypothesis improves power without leading to loss of type I error control. In this section, we perform a simulation study to assess whether such an independence assumption is reasonable in our modeling of ChIP-seq data. Specifically, we check whether the read count across all replicates is correlated with the one-sided quasi-likelihood ratio test statistic used by BinQuasi.

We repeated the data generating method of Simulation 2 (described in Section 4.2 of the main manuscript) with one modification: we removed all peaks. As a result, the null hypothesis that a window is not overlapped by a peak is always true for all windows in the partition. For each of 10 simulations, we used BinQuasi’s preprocessing steps but did not filter out any windows. Table S-1 summarizes Spearman’s correlation between the number of reads across all replicates (the filtering criterion) and BinQuasi’s test statistic for the 10 simulations. Since the correlation is near zero (mean Spearman’s correlation of 0.001), these results do not indicate dependence between BinQuasi’s filtering criterion and test statistic when the null hypothesis is true.

Table S-1: Spearman’s correlation between the number of reads across all replicates (the filtering criterion) and BinQuasi’s test statistic across 10 simulations where the null hypothesis was true for all windows.

<table>
<thead>
<tr>
<th></th>
<th>Min.</th>
<th>1st Quartile</th>
<th>Median</th>
<th>3rd Quartile</th>
<th>Max.</th>
<th>Mean</th>
<th>St. Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spearman’s correlation</td>
<td>−0.025</td>
<td>−0.010</td>
<td>0.007</td>
<td>0.011</td>
<td>0.020</td>
<td>0.001</td>
<td>0.015</td>
</tr>
</tbody>
</table>
S-2 Statistical details

In this section, we provide details of the statistical modeling and inference used in BinQuasi, our proposed peak calling method for replicates ChIP-seq data. We include details on the model for window-level counts used by BinQuasi in Section S-2.1. To introduce the testing framework, we begin with a two-sided quasi-likelihood ratio test in Section S-2.2. We then develop the one-sided quasi-likelihood ratio test used by BinQuasi for peak calling in Section S-2.3.

S-2.1 Model

BinQuasi partitions the genome into equally sized, non-overlapping windows and models the average read counts per window using a generalized linear model (GLM) framework adjusted for overdispersion via quasi-likelihood. Suppose \( Y_{ijk} \) is the observed read count for genomic window \( k = 1, \ldots, K \) in biological replicate \( j = 1, \ldots, J \) of ChIP condition \( i \) (where \( i \) denotes ChIP or input/control). Let \( c_{ij} \) denote the normalization factor for replicate \( j \) of condition \( i \), and let \( E(Y_{ijk} | c_{ij}) = \mu_{ijk} \). For the \( k \)th window, we model the dependence of the mean \( \mu_{ijk} \) on group \( i \) and replicate \( j \) using the GLM framework with a log link, as

\[
\log(\mu_{ijk}) = \beta_{0k} + \beta_{1k} I(i = \text{ChIP}) + \log(c_{ij}),
\]

where \( I(\cdot) \) is the indicator function. When adjustment for covariates is desired, additional terms can be incorporated in (1). Notice that \( \beta_{1k} \) allows for a ChIP effect: the \( k \)th window is, or is part of, a peak if \( \beta_{1k} > 0 \).

To use a quasi-likelihood approach, we will assume that the variance is a scaled function of the mean parameterized as \( \text{Var}(Y_{ijk}) = \Phi_k V_k(\mu_{ijk}) \), where \( \Phi_k > 0 \) is the unknown quasi-dispersion parameter for window \( k \). BinQuasi allows the variance function \( V_k(\mu_{ijk}) \) to be set to \( V_k(\mu_{ijk}) = \mu_{ijk} \) or \( V_k(\mu_{ijk}) = \mu_{ijk} + \omega_k \mu^2_{ijk} \), corresponding to the variance of a Poisson or negative binomial distribution, respectively. When the negative binomial distribution relationship is assumed, \( \omega_k \) is the negative binomial dispersion parameter for window \( k \). Estimates \( \hat{\omega}_k \) of \( \omega_k \) are obtained using the trended method of edgeR [5], which allows for borrowing of information between windows with similar binding profiles. Let \( \ell(\mu_{ijk} | y_{ijk}) \) or \( \ell(\mu_{ijk} | y_{ijk}, \omega_k) \) represent the quasi-likelihood function as described by McCullagh [6] under the assumption of the Poisson or negative binomial relationship, respectively. For notational simplicity, we will drop the conditioning on the estimated negative binomial dispersion \( \hat{\omega}_k \) for the remainder of this document. The corresponding quasi-likelihood function for window \( k \) is then

\[
\ell_k(\mu_k | y_k) = \sum_{i,j} \ell(\mu_{ijk} | y_{ijk}),
\]

where \( \mu_k = (\mu_{1k}, \ldots, \mu_{2,k})' \) and \( y_k = (y_{11k}, \ldots, y_{2,JK})' \). The estimated means \( \hat{\mu}_k \) are obtained by maximizing (2) using iteratively reweighted least squares to obtain the estimate \( \hat{\beta}_k \) of \( \beta_k = (\beta_{0k}, \beta_{1k})' \) in (1). The BinQuasi package for R also offers bias-reduced estimates of \( \beta_k \) found by maximizing an adjusted score equation following the procedure of Firth [1] and Kosmidis and Firth [2]. This may be particularly advantageous when maximum likelihood estimates do not exist, as is the case when all the counts in the control/input group are zero.

S-2.2 Two-sided inference

Before introducing a one-sided test, we first present the two-sided quasi-likelihood ratio test using the method of Tjur [8]. Let \( \hat{\mu}_k \) be the estimated mean vector under the restriction that \( \beta_{1k} = 0 \). An approximate test in window \( k \), corresponding to

\[
H_0 : \beta_{1k} = 0 \quad \text{versus} \quad H_1 : \beta_{1k} \neq 0,
\]

can be performed using the test statistic

\[
\text{LRT}_k = 2(\ell_k(\hat{\mu}_k | y_k) - \ell_k(\hat{\beta}_k | y_k)).
\]
Under $H_0$, LRT$_k$ converges in distribution to a scaled chi-square random variable:

$$\text{LRT}_k \xrightarrow{d} \Phi_k \chi^2_q,$$

where $q$ is the difference in dimension of the mean parameter space between the two models [6]. In the case of testing for a ChIP effect represented by $\beta_{1k}$, we have $q = 1$. This null distribution depends on the unknown quasi-dispersion parameter $\Phi_k$, which can be estimated using the deviance as

$$\hat{\Phi}_k = \frac{2(\ell_k(y_k \mid y_k) - \ell_k(\hat{\mu}_k \mid y_k))}{n - p},$$

where $p$ is the dimension of the full model mean parameter space; for the model in (1), $p = 2$. This estimate is asymptotically independent of $\hat{\beta}_k$ but may not be consistent for $\Phi_k$ when the observations are not gamma distributed, as is the case for ChIP-seq data that consist of counts [6]. For the Poisson distribution (not the negative binomial),

$$\hat{\Phi}_k \xrightarrow{d} \Phi_k \chi^2_{n - p},$$

as the counts (not the sample size) tend to infinity, a result based on the fact that the Poisson distribution converges to a normal distribution as the rate parameter goes to infinity [8].

When the estimate of the quasi-dispersion parameter has a limiting scaled chi-square distribution, Tjur [8] suggests comparing the test statistic

$$F_k = (\text{LRT}_k/q)/\hat{\Phi}_k$$

to an F distribution with $q$ and $n - p$ degrees of freedom. Due to better small sample performance, use of the deviance-based estimator of $\hat{\Phi}_k$ has been recommended for RNA-seq data [4], as opposed to an estimator based on Pearson’s statistic given by

$$\hat{\Phi}_{\text{Pearson}}^k = \frac{1}{n - p} \sum_{i,j} \frac{(Y_{ijk} - \hat{E}(Y_{ijk}))^2}{\text{Var}(Y_{ijk})}.$$ 

### S-2.3 One-sided inference (peak calling)

When the goal is detecting peaks, the two-sided test for $H_0 : \beta_{1k} = 0$ is less powerful than a one-sided test, which we present here. In the first Section S-2.3.1, we summarize relevant theoretical results from Silvapulle [7] applicable to one-sided quasi-likelihood inference in general, and then derive results for use in BinQuasi in the Section S-2.3.2.

#### S-2.3.1 Theoretical framework

Consider a general parametric model with an unknown $p$-dimensional parameter $\theta$ in a parameter space $\Theta$ that is estimated by maximizing an objective function $R_n(\theta)$, perhaps the likelihood. We present a one-sided test of

$$H_0 : R\theta = 0 \text{ vs. } H_2 : R\theta \geq 0,$$

where $R$ is a fixed matrix with $p$ columns. Let $\hat{\theta}$, $\bar{\theta}$, and $\tilde{\theta}$ denote the maximizers of $R_n(\cdot)$ over $\Theta$, \{ $R\theta \geq 0$ \}, and \{ $R\theta = 0$ \}, respectively.

Several conditions must be met to develop the desired test:

1. $R_n$ must satisfy some general regularity conditions (similar to those needed for asymptotic normality of a likelihood in an iid setting),

2. $n^{-1/2} \nabla R_n(\theta_0) \xrightarrow{d} \mathcal{N}(0, \sigma^2 W(\theta_0))$, where $\theta_0$ is the true parameter value,

3. $n^{-1} \nabla^2 R_n(\theta) \xrightarrow{p} -W(\theta),$

\[4\]
When performing a quasi-likehood ratio test in GLMs with a canonical link, the quasi-likelihood

\[
2\left(R_n(\hat{\theta}) - R_n(\tilde{\theta})\right) \overset{d}{\rightarrow} \sigma^2 \chi^2 \left\{ R|W(\theta_0)|^{-1}R', \mathbb{R}^{+q} \right\},
\]

where \( q \) is the number of inequality restrictions on \( \theta \) under \( H_0 \), \( \mathbb{R}^{+q} \) is the nonnegative orthant of \( \mathbb{R}^p \), \( \theta_0 \) is the true parameter value, and \( \chi^2 \{ \cdot \} \) denotes a chi-bar-square distribution. For any \( c \in \mathbb{R} \), the cumulative distribution function of a chi-bar-square distribution is defined as

\[
P\left( \chi^2 \left\{ R|W(\theta_0)|^{-1}R', \mathbb{R}^{+q} \right\} \leq c \right) = \sum_{i=0}^{p} w_i(p, R|W(\theta_0)|^{-1}R', \mathbb{R}^{+q}) P\left( \chi_i^2 \leq c \right),
\]

where \( w_i(\cdot) \) are non-negative weights that sum to unity and \( \chi_i^2 \) is a random variable that follows a central chi-square with \( i \) degrees of freedom. For \( i = 0 \), \( \chi_i^2 \) is taken to be a point mass at 0. From (4), it is easy to see that the chi-bar-square distribution is a mixture of chi-square distributions. While the weights \( \{ w_i(\cdot) : i = 0, \ldots, p \} \) are difficult to derive, especially for \( p > 4 \), Silvapulle offers methods of computation by simulation and a list of general properties, the most relevant of which, for our purposes, is that \( 0 \leq w_i(\cdot) \leq 0.5 \) for all \( i = 0, \ldots, p \) and any matrix \( R|W(\theta_0)|^{-1}R' \) and any space \( \mathbb{R}^{+q} \). Hence \( p = 1 \) implies \( w_0(\cdot) = w_1(\cdot) = 0.5 \).

S-2.3.2 One-sided test employed by BinQuasi

Now, we use the results from the prior section to return to the test for detecting peaks defined as

\[ H_0 : \beta_{1k} = 0 \quad \text{vs.} \quad H_2 : \beta_{1k} > 0, \]

where \( \beta_{1k} \) is as in (1) and the model is as described in Section S-2.1.

When performing a quasi-likehood ratio test in GLMs with a canonical link, the quasi-likelihood function plays the role of the objective function \( R_n(\cdot) \) and conditions (1)-(3) in Section S-2.3.1 are satisfied. In terms of the BinQuasi model, we have \( \theta = \beta_k, R_n(\cdot) = \ell_k(\cdot | \cdot), \) and \( \sigma^2 = \Phi_k \). Hence the result in (3) combined with the fact that \( \beta_{1k} \) is a scalar (i.e., \( p = 1 \)) gives

\[
\text{LRT}_k^+ = 2\left( \ell_k(\hat{\mu}_k \mid y_k) - \ell_k(\tilde{\mu}_k \mid y_k) \right) \overset{d}{\rightarrow} \Phi_k \left( \frac{1}{2} \chi_0^2 + \frac{1}{2} \chi_1^2 \right),
\]

where \( \mu_k \) is the maximizer of the quasi-likelihood under the restriction that \( \beta_{1k} > 0 \) and \( \tilde{\mu}_k \) is the maximizer of the quasi-likelihood under the restriction that \( \beta_{1k} = 0 \). Constrained estimation of \( \beta_{1k} > 0 \) is accomplished in BinQuasi using quadratic programming within each step iteratively reweighted least squares [9].

Given a consistent estimator \( \hat{\Phi}_k^{\text{consistent}} \), say, of \( \Phi_k \), we can apply Slutsky’s theorem and formulate an approximate test on

\[
\frac{\text{LRT}_k^+}{\hat{\Phi}_k^{\text{consistent}}} \overset{d}{\rightarrow} \frac{1}{2} \chi_0^2 + \frac{1}{2} \chi_1^2.
\]

Alternatively, taking an approach that is analogous to that in the general linear model, where Kudo [3] used an \( F \) distribution for one-sided likelihood ratio inference. This is accomplished by comparing

\[
\frac{\text{LRT}_k^+}{\hat{\Phi}_k}
\]

to an \( F \) distribution, a generalization of an \( F \) distribution defined for any \( c \in \mathbb{R} \) by

\[
P\left( \frac{\text{F}(p, R|W(\theta_0)|^{-1}R', \mathbb{R}^{+q})}{c} \right) \leq c \right) = \sum_{i=0}^{p} w_i(p, R|W(\theta_0)|^{-1}R', \mathbb{R}^{+q}) P\left( iF_i, \nu \leq c \right),
\]

where \( \nu \) is the degrees of freedom associated with the estimated quasi-dispersion parameter based on an unrestricted parameter space [7]. Similar to the chi-square case, \( F_{0, \nu} \) is defined as a point mass at
zero. Note the omission of the divisor $q$ in the numerator of the test statistic; this is accounted for by scaling $F_{i,\nu}$ by $i$ in the right-most probability in (5). Hence, a one-sided quasi-likelihood ratio test can be employed by comparing $\frac{\text{LRT}}{\hat{\Phi}_k}$ to the mixture distribution

$$\frac{1}{2} F_{0, n-p} + \frac{1}{2} F_{1, n-p}.$$

Typically, ChIP-seq studies have few replicates resulting in small denominator degrees of freedom $n - p$. To improve power, BinQuasi uses a shrinkage estimate of the quasi-dispersion $\hat{\Phi}_k$, computed using the approach of [4] with an initial deviance-based estimate. This allows for sharing of information across genomic windows through the use of a scaled-inverse $\chi^2$ prior distribution with $d_0$ degrees of freedom on the quasi-dispersions, and we refer the reader to [4] for additional details on this approach. As in [4], a method of moments estimate $\hat{d}_0$ of the hyperparameter $d_0$ is obtained from the distribution of the initial deviance-based estimates of $\hat{\Phi}_k$. The test used by BinQuasi that incorporates the shrinkage estimator thus compares $\frac{\text{LRT}}{\hat{\Phi}_k^{\text{shrink}}}$ to the mixture distribution

$$\frac{1}{2} F_{0, n-p+d_0} + \frac{1}{2} F_{1, n-p+d_0},$$

where $\hat{\Phi}_k^{\text{shrink}}$ is the shrinkage estimator using an initial deviance-based estimate with the unconstrained estimated mean vector $\hat{\mu}_k$ described in [4].
Section 4.2 of the main text describes Simulation 2, where 200 true peaks were assigned to chromosome 4 in *Drosophila melanogaster*. Figure S-1 shows example read coverage for the synthetic data compared to the JIL-1 dm6 data that the simulation was designed to mimic. Figure S-2 summarizes the distance between the true peak start locations and the called peak start locations.

![Graphical representation](image)

Figure S-1: Example read coverage for the synthetic data generated in Simulation 2 (bottom) compared to the JIL-1 dm6 data (top) for a 3.6kb region of chromosome 4 where a true peak (location shown in blue) was located in the simulation.
Figure S-2: Distance between the start location of true peaks to corresponding called peaks (in bp). For each true peak and method, the distance was averaged across all of the 10 simulated datasets in which a called peak intersected the true peak. Not shown: PePr, which only called one extremely wide peak.
S-4 Supplementary results for the dm6 JIL-1 analysis

This section presents additional figures comparing the overlap (Figure S-3) and biological plausibility (Figure S-4) of peaks called by BinQuasi with those called by other methods for the dm6 JIL-1 data presented in Section 5 of the main manuscript.

Figure S-3: Venn diagrams of the number overlapping peaks between BinQuasi and other methods for the JIL-1 data using default software package settings and FDR control set to 0.05. Peaks are considered called by both methods if they overlap by at least one base pair. Since it is possible for a peak called by a given method to overlap more than one peak called by BinQuasi, the overlap counts may not add to the totals reported in Table 2 of the main text.
Figure S-4: Analysis of JIL-1 data using default software package settings and FDR control set to 0.05. Distribution of distances between called peaks and the nearest transcription start site (left) and summary of the nearest mapped annotated feature to called peaks (right).
Additional real data analyses

For further comparison of peak calling methods for replicated data, four additional ChIP-seq datasets were obtained from the ENCODE project (https://www.encodeproject.org/) as bam files (Table S-2) and analyzed by the same methods used for real data in the main text. To reduce computational time, we selected one chromosome per dataset to use for comparing peak calling methods. Since chr1 is the largest, we restricted all histone modification data analyses to chr1. We only considered chr19 for the NRSF (REST) data due to the large number of non-redundant clusters identified previously in 7 human cell lines [10]. The number of peaks called, median peak width, and peak overlaps between methods are shown in Table S-3 and Figure S-5. These results indicate that BinQuasi is generally consistently conservative in calling peaks, which complements the results of Simulation 2 that indicate reasonable FDR control. Motif analysis of the TF dataset, NRSF, is performed in Section S-6.

Table S-2: Additional real datasets analyzed in this section. Abbreviations: HM, histone modification; TF, transcription factor.

<table>
<thead>
<tr>
<th>Target</th>
<th>H3K4me3</th>
<th>H3K27ac</th>
<th>H3K27me3</th>
<th>NRSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>HM</td>
<td>HM</td>
<td>HM</td>
<td>TF</td>
</tr>
<tr>
<td>Cell Line</td>
<td>HeLa-S3</td>
<td>HeLa-S3</td>
<td>HeLa-S3</td>
<td>K562</td>
</tr>
<tr>
<td>Mapping Assembly</td>
<td>hg19</td>
<td>hg19</td>
<td>hg19</td>
<td>hg19</td>
</tr>
<tr>
<td>ENCODE Experiment</td>
<td>ENCSR000AOF</td>
<td>ENCSR000AOC</td>
<td>ENCSR000ALJ</td>
<td>ENCSR000BMW</td>
</tr>
<tr>
<td># of Replicates</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Replication Type</td>
<td>Isogenic</td>
<td>Isogenic</td>
<td>Isogenic</td>
<td>Isogenic</td>
</tr>
</tbody>
</table>

Table S-3: Results for additional data analyses. Peak widths reported as medians in bp.

<table>
<thead>
<tr>
<th></th>
<th>H3K4me3 (chr1)</th>
<th>H3K27ac (chr1)</th>
<th>H3K27me3 (chr1)</th>
<th>NRSF (chr19)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Peaks Med Width</td>
<td># Peaks Med Width</td>
<td># Peaks Med Width</td>
<td># Peaks Med Width</td>
</tr>
<tr>
<td>BinQuasi</td>
<td>2,380 432</td>
<td>3,098 432</td>
<td>4,653 960</td>
<td>264 200</td>
</tr>
<tr>
<td>CisGenome</td>
<td>3,537 500</td>
<td>4,581 500</td>
<td>4,329 200</td>
<td>1,128 300</td>
</tr>
<tr>
<td>JAMM</td>
<td>36,460 157</td>
<td>24,986 209</td>
<td>177,767 52</td>
<td>14,578 72</td>
</tr>
<tr>
<td>PePr</td>
<td>3,380 4,501</td>
<td>3,743 4,501</td>
<td>0 –</td>
<td>1,669 1,401</td>
</tr>
<tr>
<td>MACS Majority</td>
<td>3,643 831</td>
<td>4,623 900</td>
<td>16,213 459</td>
<td>1,186 152</td>
</tr>
<tr>
<td>MACS Common</td>
<td>2,987 800</td>
<td>3,889 800</td>
<td>4,196 200</td>
<td>481 240</td>
</tr>
<tr>
<td>SICER Common</td>
<td>6,166 1,000</td>
<td>5,041 1,600</td>
<td>59,712 100</td>
<td>5,528 160</td>
</tr>
<tr>
<td>SICER Majority</td>
<td>22,637 800</td>
<td>14,651 800</td>
<td>163,674 150</td>
<td>27,631 240</td>
</tr>
<tr>
<td>SICER Common</td>
<td>6,166 1,000</td>
<td>5,041 1,600</td>
<td>59,712 100</td>
<td>5,528 160</td>
</tr>
</tbody>
</table>
Figure S-5: Proportion of overlap between peaks called by each method (rows) and peaks called by another method (columns). Note that no peaks were called by PePr for the H3K27me3 data.
Motif analysis of peaks called in TF datasets

To evaluate the biological plausibility of called peaks in the two real transcription factor (TF) datasets analyzed, we performed motif analysis on the hg19 NRSF data introduced in Section S-5 and the mm9 FOXA2 data introduced in Section 5 of the main text. For each method and dataset, all peaks called at the FDR level of 0.05 were extended/truncated to the central 100 bp and analyzed using HOMER software v4.9 [12] (findMotifsGenome.pl with options -size 100 -len 8).

For the NRSF (REST) data, the HOMER database motif GCMGCTGTCCATGGTGCTGA (REST-NRSF(Zf)/Jurkat-NRSF-ChIP-Seq/Homer) was the top ranking known match for all methods except for SICER Majority. For the FOXA2 data, the HOMER database motif CYTGTTTACWYW (Foxa2(Forkhead)/Liver-Foxa2-ChIP-Seq/Homer) was one of the top three ranking known matches for all methods except for PePr, which had only called five peaks for these data. Table S-4 shows the number and percentage of the truncated/extended peaks (to 100 bp) called with the NRSF or FOXA2 HOMER motif for the respective dataset. For both datasets, peaks called by BinQuasi were more highly enriched for the corresponding motif than all other methods considered, though JAMM found a higher number of peaks with the motif than BinQuasi.

Table S-4: Motif analysis of TF datasets hg19 NRSF and mm9 FOXA2. Number and percentage of peaks called (at FDR = 0.05) containing the HOMER database motif for the respective dataset in the central 100 bp of the extended/truncated peak for each method.

<table>
<thead>
<tr>
<th>Method</th>
<th>NRSF (hg19 chr19)</th>
<th>FOXA2 (mm9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Peaks Called</td>
<td># with Motif</td>
</tr>
<tr>
<td>BinQuasi</td>
<td>264</td>
<td>101</td>
</tr>
<tr>
<td>CisGenome</td>
<td>1,128</td>
<td>62</td>
</tr>
<tr>
<td>JAMM</td>
<td>14,578</td>
<td>130</td>
</tr>
<tr>
<td>PePr</td>
<td>1,669</td>
<td>20</td>
</tr>
<tr>
<td>MACS Majority</td>
<td>1,186</td>
<td>79</td>
</tr>
<tr>
<td>MACS Common</td>
<td>481</td>
<td>85</td>
</tr>
<tr>
<td>SICER Majority</td>
<td>27,631</td>
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</tr>
<tr>
<td>SICER Common</td>
<td>5,528</td>
<td>45</td>
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</table>
References


