Simultaneous Detection of Signal Regions With Applications in Genome-Wide Association Studies

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Abstract

We consider in this paper detection of signal regions associated with disease outcomes in Genome-Wide Association Studies (GWAS). Gene- or region-based methods have become increasingly popular in GWAS as a complementary approach to traditional individual variant analysis. However, these methods test for the association between an outcome and the genetic variants in a pre-specified region, e.g., a gene. In view of massive intergenic regions in GWAS and substantial interests in identifying signal regions for subsequent fine mapping, we propose a computationally efficient quadratic scan (Q-SCAN) statistic based method to detect the existence and the locations of signal regions by scanning the genome continuously. The proposed method accounts for the correlation (linkage disequilibrium) among genetic variants, and allows signal regions to have both signal and neutral variants, and the effects of signal variants to be in different directions. We study the asymptotic properties of the proposed Q-SCAN statistics. We derive an asymptotic threshold that controls for the family-wise error rate, and show that under regularity conditions the proposed method consistently selects the true signal regions. We perform simulation studies to evaluate the finite sample performance of the proposed method. Our simulation results show that the proposed procedure outperforms the existing methods, especially when signal regions have signal variants whose effects are in different directions, or are contaminated with neutral variants, or have correlated variants. We apply the proposed method to analyze a lung cancer genome-wide association study to identify the genetic regions that are associated with lung cancer risk.

Key words: Asymptotics; Correlation; GWAS; Multiple hypotheses; Scan statistics; Signal detection.

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1 Introduction

An important goal of human genetic research is to identify the genetic basis for human diseases or traits. Genome-Wide Association Studies (GWAS) have been widely used to dissect the genetic architecture of complex diseases and quantitative traits in the past ten years. GWAS uses an array technology that genotypes hundreds of thousands to millions of Single Nuclear Polymorphisms (SNPs) across the genome. GWAS has been successful for identifying thousands of common genetic variants putatively harboring SNPs associated with complex diseases [Visscher et al. 2017].

The standard analytic strategy in GWAS is to perform individual SNP tests coupled with multiple comparison adjustment and independent validation studies to identify trait- or disease-associated SNPs. Regions in the neighborhood of these GWAS-associated SNPs are subsequently finely mapped to identify causal variants pointing to molecular mechanisms behind the associations [Onengut-Gumuscu et al. 2015; Spain and Barrett 2015]. The sizes and the locations of the signal regions used for subsequent fine mapping in the neighboring genetic regions of the GWAS-associated SNPs are often arbitrarily determined. There is a substantial interest to overcome the limitations of this two-stage procedure by developing more advanced statistical methods to systematically detect signal regions in GWAS that can be used for subsequent fine mapping. Furthermore, it has been found that individual SNP analysis might be subject to power loss [Wu et al. 2010], as the effects of common variants are often weak and a large number of multiple comparisons at the SNP level in traditional GWAS analysis are needed.

Gene-based tests, as an alternative to the traditional single variant test, have become increasingly popular in recent years in GWAS analysis [Li and Leal 2008; Madsen and Browning 2009; Wu et al. 2010]. Instead of testing each SNP individually, these gene based tests evaluate the cumulative effects of multiple SNPs in a gene, and can boost power when multiple variants in the gene are associated with a disease or a trait [Han et al. 2009; Wu et al. 2010]. However, a major limitation of these gene-based tests is that one needs to pre-specify genetic regions used for analysis, e.g., genes. Hence the existing gene-based approaches are not directly applicable to association analysis in the whole genome, as there are a large number of intergenic regions across the genome, and a vast majority of variants on GWAS arrays are located in intergenic regions, which include regulatory/epigenetic regions. Indeed, gene-level analysis throws these large numbers of intergenic regions away, and hence will result in missing many signal regions. This is because many GWAS-associated SNPs that have been found in the literature are in intergenic regions and have regulatory
roles (Visscher et al. 2017). It is hence of substantial interest to develop statistical methods by going beyond traditional individual SNP analysis that can scan the genome continuously to identify the sizes and the locations of signal regions in the post-GWAS era, in order to boost analysis power and facilitate subsequent fine mapping efforts.

Scan statistics (Naus 1982) provide an attractive framework to scan the whole genome continuously for detection of signal regions in GWAS. The classical fixed window scan statistics allow for overlapping windows using a moving window of a fixed size, which “shifts forward” a window with a number of SNPs at a time and search for the windows containing signals. A limitation of this approach is that the window size needs to be pre-specified in an ad hoc way. In cases where multiple SNPs are independent in a sequence, Sun et al. (2006) proposed a region detection procedure using a scan statistic that aggregates the $p$-values of individual SNP tests. However this is not applicable to GWAS due to the linkage disequilibrium (LD), i.e., correlation, among nearby SNPs.

The mean-based scan statistic procedures have been used in DNA copy number analysis. Assuming all variants are signals with the same mean in signal regions, several authors have proposed to use the mean of marginal test statistics in each candidate region as a scan statistic. Specifically, Arias-Castro et al. (2005) proposed a likelihood ratio-based mean scan procedure in the presence of only one signal region. Zhang et al. (2010) described an analytic approximation to the significance level of this scan procedure, while Jeng et al. (2010) showed this procedure is asymptotically optimal in the sense that it separates the signal segments from the non-signals if it is possible to consistently detect the signal segments by any identification procedure. This setting is closely related to the change-point detection problem. Olshen et al. (2004) developed an iterative circular binary segmentation procedure to detect change-points, whereas Zhang and Siegmund (2007, 2012) proposed a BIC-based model selection criterion for estimating the number of change-points. However, the key assumption of these mean scan procedures that all observations have the same means in signal regions often does not hold in genetic association studies.

Indeed, although the mean based scan statistics are useful for copy number analysis, these procedures have several limitations for detecting signal regions in GWAS. Specifically, they will lose power due to signal cancellation in the presence of both trait-decreasing and trait-increasing genetic variants, or the presence of both signal and neural variants in a signal region. Both situations are common in practice. Second, they may select separate small subsets instead of the entire signal region in the presence of mixed weak signal and neutral variants in signal regions. Third, these procedures assume the individual variant test statistics are independent across the whole genome.
However, in practice, the SNPs in a genetic region are correlated due to LD.

In this paper, we propose a scaled quadratic scan statistic based procedure (Q-SCAN) to detect the existence and locations of signal regions in GWAS by scanning the whole genome continuously. Our procedure can consistently detect an entire signal segment in the presence of both trait-increasing and trait-decreasing variants and mixed signal and neutral variants. It also accounts for the correlation (LD) among the SNPs when scanning the genome. We study the asymptotic property of the proposed scan statistics. We derive a theoretical threshold which asymptotically controls the family-wise error rate. Under some regularity conditions, we also show that the proposed procedure can consistently select the exact true signal segments. We propose a computationally efficient searching algorithm for the detection of multiple non-overlapping signal regions.

We conduct simulation studies to evaluate the finite sample performance of the proposed procedure, and compare it with several existing methods. Our results show that, the proposed quadratic scan procedure outperforms the existing methods in the presence of weak signal and neutral variants, and both trait-increasing and trait-decreasing variants in signal regions. The advantage of the proposed method is more pronounced in the presence of the correlation (LD) among the SNPs in signal regions. We apply the proposed procedure to the analysis of a lung cancer GWAS dataset to identify genetic regions which are associated with lung cancer risk.

The remainder of the paper is organized as follows. In Section 2, we introduce the hypothesis testing problem and describe our proposed scan procedure and a corresponding algorithm to detect multiple signal regions. In Section 3, we present the asymptotic properties of the scan statistic, as well as the statistical properties of identifiable regions. In Section 4, we compare the performance of our procedure with other scan statistic procedures in simulation studies. In Section 5, we apply the proposed scan procedure to analyze a lung cancer GWAS dataset. Finally, we conclude the paper with discussions in Section 6. The proofs are relegated to the Appendix.

2 The Statistical Model and the Scaled Quadratic Scan Statistics for Signal Detection

2.1 Summary Statistics of Individual SNP Analysis Using Generalized Linear Models

Suppose that the data are from $M$ subjects. For the $m$th subject ($m = 1, \ldots, M$), $Y_m$ is an outcome, $X_m = (X_{m1}, \ldots, X_{mq})^T$ is a vector of $q$ covariates, and $G_{mi}$ is the $i$th of $n$ SNPs in the genome. One constructs individual SNP test statistics in GWAS by regressing $Y_m$ on each SNP $G_{mi}$ adjusting
for the covariates $X_m$. Conditional on $(X_m, G_{mi})$, $Y_m$ is assumed to follow a distribution in the exponential family with the density $f(Y_m) = \exp \left\{ Y_m \theta_m - b(\theta_m) + c(Y_m, \phi) \right\}$, where $a(\cdot)$, $b(\cdot)$ and $c(\cdot)$ are some known functions, and $\theta_m$ and $\phi$ are the canonical parameter and the dispersion parameter, respectively \cite{McCullagh and Nelder 1989}. Denote by $\eta_m = E(Y_m|X_m, G_{mi}) = b'(\theta_m)$.

The test statistic for the $i$th SNP is constructed using the following Generalized Linear Model (GLM) for the $i$th SNP \cite{McCullagh and Nelder 1989}

$$g(\eta_m) = X_m^T \alpha + G_{mi} \beta_i,$$

where $g(\cdot)$ is a monotone link function. For simplicity, we assume $g(\cdot)$ is a canonical link function.

The variance of $Y_m$ is $\text{var}(Y_m) = a_m(\phi) v(\eta_m)$, where $v(\eta_m) = b''(\theta_m)$ is a variance function.

Let $\hat{\eta}_0 = g^{-1}(X_m^T \hat{\alpha})$, where $\hat{\alpha}$ is the Maximum Likelihood Estimator (MLE) of $\alpha$, and $\hat{\phi}$ is the MLE of $\phi$, both under the global null model of $g(\eta_m) = X_m^T \alpha$. Assume $\Lambda = \text{diag} \left\{ a_1(\hat{\phi}) v(\hat{\eta}_01), \ldots, a_M(\hat{\phi}) v(\hat{\eta}_0M) \right\}$ and $P = \Lambda - \Lambda X (X^T \Lambda X)^{-1} X^T \Lambda$ where $X = (X_1, \ldots, X_M)^T$. The marginal score test statistic for $\beta_i$ of the $i$th SNP is

$$Z_i = G_i^T (Y - \hat{\eta}_0) / \sqrt{G_i^T P G_i},$$

where $G_i = (G_{i1}, \ldots, G_{iM})^T$ denotes the $i$th SNP data of $M$ subjects, $\hat{\eta}_0 = (\hat{\eta}_{01}, \ldots, \hat{\eta}_{0M})^T$ and $Y = (Y_1, \ldots, Y_M)^T$. These individual SNP test statistics are asymptotically jointly distributed as $Z \sim N(\mu, \Sigma)$, where $Z = (Z_1, \ldots, Z_n)^T$, $\mu = E(Z)$. Note that $\mu = 0$ under the global null of all $\beta_i$ being 0, and $\Sigma_{ii'}$ can be estimated by

$$\hat{\Sigma}_{ii'} = G_i^T P G_i / \left( G_i^T P G_i^T P G_i \right).$$

These individual SNP summary statistics $Z_i$ are often available in public domains or provided by investigators to facilitate meta-analysis of multi-cohorts.

Region-level analysis has become increasingly important in GWAS \cite{Li and Leal 2008, Wu et al. 2010} as a complementary tool to conventional individual SNP analysis to boost analysis power and identify signal regions for subsequent fine mapping. We develop in the next section a scaled quadratic scan statistic using the summary statistics $Z_i$ to scan the whole genome continuously to detect the existence and locations of the signal regions that are associated with diseases and traits. The proposed statistic allows for signal variants to have effects in different directions and mixed with neural variants in signal regions, and accounts for between-SNP correlation (LD) in each candidate region.
Let a sequence of \( n \) marginal test statistics be \( Z = \{Z_1, \ldots, Z_n\} \), where \( Z_i \) is the marginal test statistic at location \( i \) and \( n \) is the total number of locations, e.g., the total number of SNPs in GWAS. We assume that the sequence \( Z \) follows a multivariate normal distribution

\[
Z \sim N(\mu, \Sigma),
\]  

(2)

where \( \mu \) is an unknown mean of \( Z \) and \( \Sigma = \text{cov}(Z) \). This normality assumption of the summary statistics \( Z_i \) is reasonable in GWAS, as GWAS often has large sample sizes and genotypes common variants. Under the global null hypothesis of no signal variant across the genome, we have \( \mu = 0 \).

Under the alternative hypothesis of non-overlapping signal regions, there exist signals in certain non-overlapping regions \( I^*_1, \ldots, I^*_r \) satisfying \( \mu_{I^*_j} \neq 0 \), where \( \mu_{I^*_j} = \{\mu_i\}_{i \in I^*_j} \) and the \( \{\mu_i\}_{i \in I^*_j} \) can have different directions and magnitudes with some being allowed to be zero for each signal region \( I^*_j \) (\( j = 1, \ldots, r \)). Note the lengths of the signal regions \( I^*_j \) are allowed to be different. Specifically, we define region \( I^*_j \) as a signal segment if it satisfies the following two conditions. First, in a large area that contains \( I^*_j \), there is no signal point \( (\mu \neq 0) \) outside \( I^*_j \). This condition is defined rigorously in the regularity condition (D) in Section 3. Second, the standardized signal strength of \( I^*_j \) is larger than that of any subregion of \( I^*_j \). The second condition is defined rigorously in the regularity condition (C) in Section 3. Denote a collection of the non-overlapping signal regions by \( \mathcal{I} = \{I^*_1, \ldots, I^*_r\} \). Our goal is to detect whether any signal segments exist, and if they do exist, to identify the locations of these segments. Specifically, we first test

\[
H_0 : \mathcal{I} = \emptyset \quad \text{against} \quad H_1 : \mathcal{I} \neq \emptyset.
\]  

(3)

If \( H_0 \) is rejected, detect each signal region in \( \mathcal{I} \).

A scan statistic procedure tackles the hypothesis testing problem (3) by using the maximum value of the scan statistics of all possible regions,

\[
Q_{\max} = \max_{|I| \leq C_n} Q(I),
\]  

(4)

where \( Q(I) \) is the scan statistic for region \( I \), \( |I| \) denotes the length of \( I \), and \( C_n \) is the largest searching window length. A large value of \( Q_{\max} \) indicates evidence against the null hypothesis. If the null hypothesis is rejected, the selected signal region is \( \hat{I} = \arg\max_{|I| \leq C_n} Q(I) \).

Jeng et al. (2010) and Zhang et al. (2010) proposed a scan procedure based on the mean of the marginal test statistics of a candidate region (M-SCAN). The mean scan statistic for region \( I \) is

\[
Q_I = \frac{1}{n} \sum_{i \in I} Z_i.
\]
defined as

\[ Q(I) = \sum_{i \in I} Z_i / \sqrt{|I|}. \]  

(5)

When the test statistics \( Z_i \) are independent (\( \Sigma = I_n \)) with a common mean in a signal region (\( \mu_i = \mu \) for all \( i \in I_j \)), Arias-Castro et al. (2005) and Jeng et al. (2010) showed that the mean scan procedure is asymptotically optimal in the sense that it separates the signal segments from the non-signals as long as the signal segments are detectable. However, in GWAS, the assumption that marginal tests \( Z_i \) are independent and have the same mean in signal regions do not hold. This is because, first, nearby SNPs are correlated due to LD and hence the marginal test statistics in a region are usually correlated; second, signal SNPs in a signal region are likely to have effects in different directions and be mixed with neutral variants. Hence application of the existing mean scan statistics (5) for detecting signal regions in GWAS is likely to not only yield invalid inference due to failing to account for correlation between the \( Z_i \)'s across the genome, but also more importantly lose power due to cancellation of signals in different directions in signal regions.

2.3 The Scaled Quadratic Scan Procedure

To overcome the limitations of the mean scan procedure, we propose a scaled quadratic scan procedure (Q-SCAN) that selects signal regions based on the sum of quadratic marginal test statistics, which is defined as,

\[ Q(I) = \sum_{i \in I} (Z_i^2 - 1) / |I|^{\gamma}, \]  

(6)

where \( \gamma > 0 \) is a constant. When the marginal test statistics \( Z_i \) are independent, the scan statistic \( Q(I) \) in (6) corresponds to the likelihood ratio statistic for testing \( H_0 : \mu_I = 0 \) versus \( H_1 : \mu_I \neq 0 \) for a given region \( I \), and follows a (scaled) centered chi-square distribution with \( |I| \) degrees of freedom under the null. In the presence of correlation among the test statistics \( Z_i \)'s, the null distribution of \( Q(I) \) is a centered mixture of chi-squares \( \sum_{j=1}^{|I|} w_j (\chi^2_{1j} - 1) \), where the \( \chi^2_{1j} \) are independent chi-square random variables with one degree of freedom, and the weights are \( w_j = \lambda_j / |I|^{\gamma} \), where the \( \lambda_j \) are the eigenvalues of the covariance matrix \( \Sigma_I \) of the \( \{Z_i\}_{i \in I} \)'s. When signals have different directions in a signal region, the proposed Q-SCAN statistic avoids signal cancellation that will result from using the mean scan statistic (5).

The scale constant \( |I|^{\gamma} \) is used to normalize the numerator in (6) so that \( Q(I) \) will not increase purely by increasing the length of a region. This will avoid larger regions from always being chosen when maximizing \( Q(I) \) for different \( I \)'s. We need to properly choose the scale parameter
γ to ensure the scan statistics $Q(I)$ are comparable for different region lengths. Specifically, the unscaled quadratic scan statistic ($\gamma = 0$) is not desirable as it increases with $|I|$ and hence always prefers larger regions. This results in choosing the regions whose lengths are close to $C_n$. When $\gamma = 1$, $Q(I)$ always chooses a single signal point instead of a signal region. The reason is that
\[
\max_{|I| \leq C_n} \sum_{i \in I} \{Z_i^2 - 1\} / |I| = \max_{1 \leq i \leq n} (Z_i^2 - 1).
\]
We show in Section 3 that when $\gamma \in (0, 0.5)$, the proposed scaled Q-SCAN procedure is consistent for detecting signal segments under mild conditions. Our numerical results show the proposed procedure is robust to the choice of $\gamma$ when $0 < \gamma < 1/2$.

We reject the null hypothesis (3) if the scan statistic of a region is larger than a given threshold. If this results in only one region, the estimated signal region is $\hat{I} = \arg\max_{|I| \leq C_n} Q(I)$. If this results in multiple overlapping regions, we estimated the signal region as the interval whose scan statistic is greater than the threshold and achieves the local maximum in the sense that the scan statistic of that region is greater than the regions that overlap with it. We propose a searching algorithm to consistently detect true signal regions in the next section.

### 2.4 Searching Algorithm for Multiple Signal Regions

In general, there might be several signal regions in a whole genome. We now describe an algorithm for detecting multiple signal regions. Motivated by GWAS, we assume the signal regions are short relatively to the size of the whole genome, and are reasonably well separated. Hence intuitively, the scan statistic for proper signal region estimation should achieve a local maximum. Following [Jeng et al., 2010] and [Zhang et al., 2010], our proposed searching algorithm first finds all the candidate regions with the scaled quadratic scan statistic greater than a pre-specified threshold $h(n, C_n)$. Then we select the intervals from the candidate sets that have the largest scan statistic than the other overlapped intervals in the candidate set as the estimated signal regions. The detailed algorithm is given as follows:

**Step 1.** Set the largest searching window length $C_n$ and calculate $Q(I)$ for the intervals with length less than or equal to $C_n$.

**Step 2.** Pick the candidate set
\[
\mathcal{T}^{(1)} = \{I : Q(I) > h(n, C_n), |I| \leq C_n\}
\]
for some threshold $h(n, C_n)$. If $\mathcal{T}^{(1)} \neq \emptyset$, we reject the null hypothesis, set $j = 1$ and proceed with the following steps.
Step 3. Let \( \hat{I}_j = \text{argmax}_{I \in \mathcal{I}(j)} Q(I) \), and update \( \mathcal{I}(j+1) = \mathcal{I}(j) \setminus \{ I \in \mathcal{I}(j) : I \cap \hat{I}_j \neq \emptyset \} \).

Step 4. Repeat Step 3 and Step 4 with \( j = j + 1 \) until \( \mathcal{I}(j) \) is an empty set.

Step 5. Define \( \hat{I}_1, \hat{I}_2, \cdots \) as the estimated signal regions.

After the scan statistic \( Q(I) \) is calculated for each region \( |I| \leq C_n \), we can estimate the null distribution of \( Q_{\text{max}} \). A threshold \( h(n, C_n) \) is set based on the null distribution of \( Q_{\text{max}} \). Specifically, the threshold \( h(n, C_n) \) is calculated to control for the family-wise error rate at a desirable level by adjusting for multiple testing of all searched regions. Section 3.1 provides detailed discussions on calculating \( h(n, C_n) \) theoretically and empirically.

Steps 3-4 are used to search for all the local maximums of the scan statistic \( Q(I) \) by iteratively selecting the intervals from the candidate set with the largest scan statistics \( Q(I) \), and then deleting a selected signal interval and any other intervals overlapping with it from the candidate set before moving on to select the next signal interval. Step 5 collects all the local maximums as the set of selected signal regions. The intuition of this algorithm is as follows. Since we assume the signal segments are well separated in the sequence, for a signal region, no region with length less than or equal to \( C_n \) overlaps with more than one signal region. Thus the test statistic of a signal region \( I \) is larger than the other intervals that overlap with it. It follows that a local maximum provides good estimation of a signal region.

Selection of the largest searching window length \( C_n \) is an important issue in scan procedures. Specifically, \( C_n \) should be larger than the lengths of all signal regions to ensure that each signal region will be searched. In the meantime, \( C_n \) should be smaller than the shortest gap between signal regions to ensure that no candidate region \( I \) with \( |I| \leq C_n \) overlaps with two or more signal regions. The parameter \( C_n \) also determines computation complexity. A smaller \( C_n \) requires less computation. In practice, we choose the largest searching window length \( C_n \) based on the lengths of genes and LD blocks across the chromosomes.

3 Asymptotic Properties of the Scaled Quadratic Scan Procedure

In this section, we present two theoretical properties of the Q-SCAN procedure. The first property is that, under the null hypothesis in (3), the Q-SCAN procedure using a theoretical threshold asymptotically controls the family-wise error rate. The second property shows that, under certain regularity conditions, the Q-SCAN procedure consistently selects the exact signal regions using the theoretical threshold.
3.1 Family-wise Error Rate Control

Let \( \hat{I} = \{ \hat{I}_1, \hat{I}_2, \ldots \} \) be a collection of estimated signal regions. To investigate whether the Q-SCAN procedure can control for the family-wise error rate at level \( \alpha \), we need to find a theoretical threshold \( h(n, C_n) \) such that asymptotically,

\[
P_{H_0}\{Q_{\text{max}} > h(n, C_n)\} \leq \alpha.
\]

The following theorem gives the convergence rate of \( Q_{\text{max}} \), which facilitates calculating the theoretical threshold \( h(n, C_n) \).

**Theorem 1** Suppose that the centered, stationary Gaussian process \( \{Z_j\}_{j \geq 1} \) has a spectral density function \( f(s) \in L^q(ds) \) for some \( 2 < q \leq \infty \), where \( L^q(ds) = \{ f : (\int |f|^q)^rac{1}{q} < \infty \} \). Assume \( \{Z_j\}_{j \geq 1} \) is \( M_n \)-dependence where \( \log(M_n) = o(\log n) \). Let \( C_n \) is a sequence satisfying \( \lim_{n \to \infty} \log n/C_n^{1-2\gamma} > 0 \) with \( 1/q < \theta < 1/2 \). Then for any \( \gamma < \theta - 1/q \), we have

\[
Q_{\text{max}}/\sqrt{2\sigma^2 C_n^{1-2\gamma} \log n} \overset{P}{\to} 1.
\]

where \( \sigma^2 = \int_0^{2\pi} f^2(s) ds/\pi \).

**Remark 1** Under the assumption of a stationary sequence, we have \( \Sigma = \{\sigma_{ij}\} = \{\rho_{|i-j|}\} \), we have

\[
\sigma^2 = \lim_{n \to \infty} \frac{1}{n} \sum_{j=1}^{n} \lambda_j^2 = 2 + 4 \lim_{n \to \infty} \sum_{k=1}^{n-1} (1 - k/n) \rho_k^2
\]

where \( \lambda_1, \ldots, \lambda_n \) are the eigenvalues of \( \Sigma \).

The proof of Theorem 1 is provided in the Appendix. Theorem 1 gives the convergence rate of \( Q_{\text{max}} \). Using this result, we can define the theoretical threshold as

\[
h(n, C_n) = (1 + \epsilon)\sqrt{2\sigma^2 C_n^{1-2\gamma} \log n}
\]

for a small \( \epsilon > 0 \). This choice of \( h(n, C_n) \) ensures \( P_{H_0}\{Q_{\text{max}} > h(n, C_n)\} \leq \alpha \) and hence asymptotically control the family-wise error rate.

In GWAS, the number of SNPs \( n \) is large, e.g., from hundreds of thousands to millions. However, \( \log n \) grows much slower and is comparable to the lengths of genes or LD blocks, so that the condition of \( C_n \) is reasonable in practice. Further, two marginal test statistics are independent when two SNPs are sufficiently far apart in the genome, the assumption of \( M_n \) dependence is reasonable for GWAS. Note all the existing scan methods assume independence of marginal tests. Our results are
stronger than the existing results by allowing for correlation among SNPs assuming a stationary structure.

Although Theorem 1 shows that the family-wise error rate can be asymptotically controlled, it is difficult to use the theoretical threshold for an exact \( \alpha \)-level test in practice. We propose to use Monte Carlo simulations to determine an empirical threshold to control the family-wise error rate at the \( \alpha \)-level. Specifically, we generate samples from \( N(0, \Sigma) \) and calculate \( Q_{\text{max}} \). We repeat this for \( N \) times and use the \( 1 - \alpha \) quantile of the empirical distribution as the data-driven threshold. Section 4 presents details on calculating the empirical threshold.

3.2 Power analysis

Let \( \mathbf{\mu}_I = \{ \mu_i \}_{i \in I} \) for any region \( I \) and \( \| \mathbf{\mu}_I \|_2 = \sqrt{\sum_{i \in I} \mu_i^2} \) be the \( L_2 \) norm of \( \mathbf{\mu}_I \). Assume \( I^* = (\tau_1^*, \tau_2^*) \) be the signal segment and \( p_n = |I^*| \) be the number of variants in region \( I^* \). Let \( \Sigma_k \) be the \( k \)th order leading principle sub-matrix of \( \Sigma \) and \( \lambda_{k, \text{max}} \) be the maximum eigenvalue of \( \Sigma_k \). Denote by \( h(n, C_n) \) the theoretical threshold defined by (7). Before stating our main results, we first introduce the following regularity conditions for the signal region.

(A) \( \| \mathbf{\mu}_{I^*} \|_2^2 \geq (1 + \epsilon + \delta_n)p_n^2\sqrt{2\sigma^2C_n^{4-2\gamma}\log n} \) for some \( \delta_n \) such that \( \delta_n\sqrt{\log n} \to \infty \),

(B) \( \| \mathbf{\mu}_{I^*} \|_2^2 > \sqrt{2\sigma^2p_n^{3/2}(\log p_n)^2}\lambda_{p_n, \text{max}}, \)

(C) \( \| \mathbf{\mu}_{I^*} \|_2^2/\sqrt{|I^*|} \geq \max_{I \subseteq I^*} \| \mathbf{\mu}_I \|_2^2/\sqrt{|I|} \),

(D) There exists \( \tau \geq C_n \), which \( C_n \) is the largest searching window length, such that \( \mathbf{\mu}_{I^*} \neq 0 \) and \( \mathbf{\mu}_{I_1} = \mathbf{\mu}_{I_2} = 0 \) where \( I_1 = (\tau_1^* - \tau, \tau_1^*) \) and \( I_2 = (\tau_2^*, \tau_2^* + \tau) \).

Conditions (A) and (B) impose on the signal strength of the signal region. Condition (A) is similar to the condition assumed in [Jeng et al. (2010)] and ensures that the signal region \( I^* \) will be selected in the candidate set \( \mathcal{I}^{(1)} \), which means that the test statistic of \( I^* \) is larger than the threshold. Condition (B) specifies the growth rate of the average of signal strength, which is implied by condition (A) when \( p_n = O\{ (\log n)^{2/3} \} \). For each signal variant \( i \), by our definition, \( \mu_i = E(Z_i) = O(\sqrt{M}) \), where \( M \) is the sample size. In GWAS, the sample size is always large and thus conditions (A) and (B) are reasonable in reality. Condition (C) specifies the signal region in terms of its standardized signal strength. It means that a signal region is defined in such a way that its average signal strength is larger than that of any of its sub-regions. This definition allows a signal region to consist of both signal and neutral variants, which is more realistic and commonly
the case in GWAS. This condition is implicitly assumed when signals have the same strength. However the common strength assumption that is suitable for CNV studies is inappropriate for GWAS.

Condition (C) also holds when the sparsity parameter is constant in the signal region. To be specific, let $s(I)$ be the number of signals in region $I$, i.e., the number of $\mu_i$’s that are not zero in region $I$. Assume $s(I) = p^\xi(I)$, where $\xi(I) = \xi^*$ is the sparsity parameter of region $I$. Denote by $d(I) = ||\mu_I||_2^2/s(I)$ the average signal strength of region $I$. Although signals are sparse across the genome, we assume that signals are dense in the signal region (Donoho and Jin 2004; Wu et al. 2011). The average strength of signals in the true signal region should be larger than that of any subregion of the true region, that is, $||\mu_{I^*}||_2^2/|I^*|^\frac{1}{2} \geq \max_{I \subseteq I^*} ||\mu_I||_2^2/|I|^{1/2}$, which indicates that condition (C) holds. Condition (D) assumes that there is no signal point ($\mu_i \neq 0$) outside $I^*$ in a large area that contains $I^*$.

The following theorem states our main result.

**Theorem 2** Assume the same conditions as in Theorem 1 and (7) hold. Suppose condition (A) holds, then we can consistently select a signal region that overlaps with the true signal region,

$$P_{H_1}\{Q(I^*) > h(n, C_n)\} \rightarrow 1.$$  \hfill (8)

If in addition, condition (B) and (C) hold, we have

$$P_{H_1}\left[\max_{I \cap I^* \neq \emptyset, I \neq I^*} \{Q(I) - Q(I^*)\} > 0\right] \rightarrow 0.$$  \hfill (9)

Combine (8) and (9), we have

$$P_{H_1}(I^* \in \hat{I}) \rightarrow 1.$$ 

This means the scaled quadratic scan procedure consistently selects the true signal region. When there are multiple signal regions, by using Theorem 2, Q-SCAN could consistently select all signal regions. Details are provided in the Appendix.

**Remark 2** When the marginal test statistics $Z_i$ are independent, we have $\lambda_{p_n,\max} = 1$ in condition (B) and could replace $3 + 2\sqrt{2}$ by 4 in condition (C).

The proof of Theorem 2 is provided in the Appendix. The results in Theorem 2 show that the proposed scaled quadratic scan procedure is consistent for estimating a signal region, and its consistency depends on the signals only through their $L_2$ norm. This indicates that the direction
and sparsity of the signals in a signal region do not affect the consistency of the proposed scan procedure.

When marginal test statistics are independent and signals have the same strength in the signal region, i.e., $\mu_i = \mu$ for all $i \in I^*$, Jeng et al. (2010) developed a theoretically optimal likelihood ratio selection procedure based on the mean scan statistic (5). For the likelihood ratio selection procedure to consistently detect the signal region $I^*$, the condition on $\mu$ is

$$\mu \geq \sqrt{2(1 + \delta_n)} \log n / \sqrt{p_n}$$

for some $\delta_n$ such that $\delta_n \sqrt{\log n} \to \infty$. It means that $||\mu_{I^*}||_2^2 \geq 2(1 + \delta_n) \log n$. This condition is weaker than condition (A) in Theorem 2, which is $||\mu_{I^*}||_2^2 \geq 2(1 + \epsilon + \delta_n) \log n (p_n C_n^{-\gamma} \sqrt{C_n^{1-2\theta} / \log n})$ for this situation. However, it is obvious that the Q-SCAN procedure has more power than the mean scan procedure (Jeng et al. 2010) in the presence of both trait-increasing and trait-decreasing variants in the signal region. Q-SCAN is also more powerful in the presence of weak or neutral variants in the signal region. We will illustrate this in finite sample simulation studies in Section 4.

4 Simulation Studies

4.1 Family-wise Error Rate for Scaled Quadratic Scan Procedure

In order to validate the proposed Q-SCAN procedure in terms of protecting family-wise error rate using the empirical threshold, we estimated the family-wise error rate through simulation. To mimic GWAS data, we simulated the variants on Chromosome 15 using the LD structure from the CEU population in the HapMap project using Hapgen2 (Su et al. 2011) and took one of every 12 variants as the typed genotypes. Here we only consider the common variants with minor allele frequency greater than 0.05. The total sample size $M$ is set to be 2000, 4000 or 8000 and the corresponding number of variants in Chr15 used for analysis are 15416, 15334 and 15450, respectively. We first consider the continuous phenotype generated from the model:

$$Y = 0.5X_1 + 0.5X_2 + \epsilon,$$

where $X_1$ is a continuous covariate generated from a standard normal distribution, $X_2$ is a dichotomous covariate taking values 0 and 1 with a probability of 0.5, and $\epsilon$ follows a standard normal distribution. We selected the largest searching window length $C_n = 50$. We scanned the whole chromosome and controlled the family-wise error rate at 0.05 level with the empirical threshold. The empirical threshold was calculated based on Monte Carlo simulations. For each simulated data set, we estimated $\Sigma$ using (1) and generated random variables $z_i$’s from $N(0, \hat{\Sigma})$. Note that as the chromosome-wide estimated $\hat{\Sigma}$ might be singular, we simulated the $z_i$’s as follows. We first
generated $u \sim N(0, I_M)$. Let $P = \Omega^T \Lambda \Omega$ be the singular value decomposition of $P$. Assume $l_i$ be the $L_2$ norm of the $i$th row of $G^T \Omega^T \Lambda^{1/2}$, the sequence diag$(l_1^{-1}, \cdots, l_n^{-1})G^T \Omega^T \Lambda^{1/2}u$ follows the distribution $N(0, \hat{\Sigma})$. Then we calculated the extreme value $Q_{max}$ of the scan statistic $Q(I) = \sum_{i \in I}(Z_i^2 - 1)/|I|^\gamma$ using (4) across the chromosome. Note that although $\hat{\Sigma}$ is singular across the chromosome, only the covariance of size $C_n$ affects the scan statistic $Q(I) and $C_n \ll n$. The estimated covariance $\Sigma_I$ of any $Q(I)$ for $|I| < C_n$ is full rank and can be reliably estimated. To compute the empirical threshold for each simulated data set, we repeated this chromosome-wide MC simulations for 2000 times and used the 95% quantile of the empirical distribution of $Q_{max}$ as the empirical threshold. The simulation was repeated for 10000 times.

We also conducted the family-wise error rate simulations for dichotomous phenotypes using similar settings except that the dichotomous outcomes were generated via the model:

$$\text{logit}\left\{Pr(Y_m = 1)\right\} = -2.2, \ m = 1, \cdots, M,$$

which means the prevalence is set to be 0.1. Case-control sampling was used and the numbers of cases and controls were equal. The sample sizes were the same as those used for continuous phenotypes.

For both continuous and dichotomous phenotype simulations, we applied the scaled quadratic scan procedure with the scale parameter $\gamma = 1/4, 1/3$ or $1/2$ and the unscaled quadratic scan procedure ($\gamma = 0$ in (6)) to each of the 10000 data sets. Table 1 summarizes the simulation results. In each setting, the family-wise error rate is accurate at the 0.05 significance level and all the empirical family-wise error rate fall in the 95% confidence interval of the 10000 Bernoulli trials with probability 0.05. These results showed that both the scaled and unscaled quadratic scan procedures are valid methods and protect the family-wise error rate.

4.2 Power and Detection Accuracy Comparisons for Different Correlation and Signal Structure

In this section, we performed simulation studies to study the power of the proposed scaled quadratic scan method Q-SCAN in finite samples, and compared its performance with several other methods, including the mean scan method M-SCAN and the unscaled quadratic statistic statistic ($\gamma = 0$ in (6)). We selected the scale parameter $\gamma = 1/4, 1/3$ or $1/2$ in Q-SCAN. For each simulated data set, we generated $n = 10000$ individual test statistics, and the observations $\{z_i\}_{1 \leq i \leq n}$ were generated from a multivariate normal distribution $N(\mu, \Sigma)$. Three different correlation structures were considered:
Independent: The individual test statistics are independent, that is, $\Sigma = I_n$.

Banded: The correlation matrix of individual test statistics is banded, that is, $\Sigma = (\sigma_{ij})$ with $\sigma_{ij} = \rho \mathbf{I}(1 < |j-i| \leq B) + \mathbf{I}(i=j)$, where $B = 3$ is a bandwidth and $\rho = 0.35$.

AR(1): The correlation matrix of individual test statistics is AR(1), that is, $\Sigma = (\sigma_{ij})$ and $\sigma_{ij} = \rho^{|i-j|}$ where $\rho = 0.6$.

For each setting, 2000 simulated datasets were generated.

We considered three signal segments $I_1, I_2, I_3$ with each having a length $|I_j| = 13$. We selected the maximum searching window length $C_n = 39$. We considered the following three different signal structures in the signal regions $I_1, I_2, I_3$:

Signal structure 1 (Homogeneous signals): All the SNPs in each signal region are signals with the common mean, i.e., $\mu_i = \mu$ ($i = 1, \cdots, 13$).

Signal structure 2 (Heterogeneous signals): All the SNPs in each signal region are signals with the same magnitude but different directions as $\mu_i = \mu$ for $i \neq 3, 7, 11$ and $i \in [1, 13]$, and $\mu_i = -\mu$ for positions $i = 3, 7, 11$.

Signal structure 3 (Mixed signals and noises): Signal SNPs are mixed with neutral SNPs in each signal region. Specifically, the SNPs in the odds positions are signals with the same magnitude but different directions as $\mu_i = \mu$ for $i = 1, 5, 9, 13$ and $\mu_i = -\mu$ for position $i = 3, 7, 11$, while the SNPs in the even positions are neutral, i.e., $\mu_i = 0$ if $i$ is an even number ($i = 1, 2, \cdots, 13$).

We used the empirical threshold to control for the family-wise error rate at the exact $\alpha_0 = 0.05$ level. The empirical threshold was based on Monte Carlo Simulations. For each step, we generated samples from $N(0, \Sigma)$ and calculated the extreme value $Q_{\text{max}}$ of the test statistic $Q(I) = \sum_{i \in I} (Z_i^2 - 1)/|I|^{\gamma}$ across the genome with the given $C_n$. For each simulated data set, we performed Monte Carlo simulations 2000 times, and calculated the empirical threshold using the $1 - \alpha_0$ quantile of the empirical distribution of $Q_{\text{max}}$. We varied $\mu$ to study power changes.

For M-SCAN, we used $|\sum_{i \in I} Z_i|/\sqrt{\text{var}(\sum_{i \in I} Z_i)}$ as the scan statistic to account for the LD among SNPs, where the denominator accounts for the correlation among the $Z_i$. To make the comparison meaningful, we used the same searching algorithm and the Monte Carlo simulations based empirical threshold for M-SCAN.
To evaluate the powers for these methods, we used the signal points detection rate and sensitivity as performance measurements, which are defined as

\[
\text{Signal Points Detection Rate} = \frac{|A \cap (\bigcup_j \hat{I}_j)|}{|A|}, \quad \text{Sensitivity} = \frac{\sum_{k=1}^3 |I_k \cap (\bigcup_j \hat{I}_j)|}{\sum_{k=1}^3 |I_k|},
\]

where \( A = \{ i : \mu_i \neq 0 \} \) is the set of signal points. Note that, sensitivity would be the same as signal points detection rate when all the points are signals in a signal region. Hence these two values are equal in the presence of homogeneous and heterogeneous signals in signal structures 1 and 2. We omit comparing specificity, as signals are sparse across the entire long sequence across the genome, thus specificity is always nearly 1 and the differences in specificity between different procedures are small and are not informative.

A limitation of using signal points detection rate and sensitivity as performance measurements is that both measures are 1 if a very large segment that includes a signal region is used, e.g, by simply using the whole genome as a segment. They are hence not informative for measuring the accuracy of the estimated signal location. Following Jeng et al. (2010) and Jeng et al. (2013), we also evaluated the accuracy of estimating the location of each signal segment \( I_k \) using the dissimilarity measure

\[
D(I_k) = \min_j \left\{ \frac{1 - |\hat{I}_j \cap I_k|}{(|\hat{I}_j||I_k|)^{\frac{1}{2}}} \right\}.
\]

A lower value of the dissimilarity measure implies more accurate estimation of the location of the signal region. Specially, \( D(I_k) = 0 \) means that we can detect the exact location of the signal region \( I_k \), and \( D(I_k) = 1 \) means that there is no detected signal region that overlaps with the true signal region \( I_k \). We calculate the dissimilarity measure \( D(I_k) \) for each signal region \( I_k \), \( k = 1, 2, 3 \) in the sequence and report the average dissimilarity measure over all three signal regions, i.e, \( \frac{D(I_1) + D(I_2) + D(I_3)}{3} \).

We also proposed to use the kappa value to evaluate both power and accuracy of all the estimated locations of signal regions simultaneously,

\[
\kappa = \left\{ \frac{Pr(a) - Pr(e)}{1 - Pr(e)} \right\} / 1 - Pr(e),
\]

where \( Pr(a) = |\mathcal{I} \cap \hat{\mathcal{I}}| + |\mathcal{I}^c \cap \hat{\mathcal{I}}^c| / n \) and \( Pr(e) = (n - |\mathcal{I}|)(n - |\hat{\mathcal{I}}|)/n^2 + |\mathcal{I}||\hat{\mathcal{I}}|/n^2 \), \( \mathcal{I} \) is a collection of true signal regions and \( \hat{\mathcal{I}} \) is a collection of estimated signal regions. Kappa value measures the degree of agreement of the true and estimated signal regions. A higher value of kappa value implies a procedure provides more accurate estimation of true signal regions and less falsely detected non-signal regions. For example, \( \kappa = 1 \) means that the regions detected by a procedure contain all the
true signal regions with the exact locations, and do not contain any null (no-signal) regions. Unlike the other three criteria that only consider the detected regions that overlap with the true signal regions, the kappa value also takes into account of the detected regions that do not overlap with true signal regions and hence provides a more comprehensive measure of the accuracy of the signal region detection.

Figure 1 summarizes the simulation results when signals are homogeneous (Signal Structure 1) and the correlation matrix of individual tests is AR(1). In this situation, Q-SCAN with $\gamma = 1/4$ had a better performance for detecting signal regions than the other procedures. It had a higher kappa value and a lower dissimilarity measure than the other procedures. It also had a comparable power with the unscaled quadratic scan procedure, which had the highest power measured using signal points detection rate and sensitivity. The performance of Q-SCAN with $\gamma = 1/3$ was similar and only slightly worse than that with $\gamma = 1/4$. This indicates the results are not sensitive to the choice of $\gamma$ when $\gamma < 1/2$. Note that although the unscaled quadratic scan procedure had the highest power, its dissimilarity measure remained the same when the signal strength $\mu$ increased. This finding indicated that the unscaled quadratic scan procedure tended to select a larger region than the true signal region. Also note that, instead of decreasing to 0, the dissimilarity measure of M-SCAN largely unchanged as the signal strength increased. This implied that M-SCAN failed to detect the true locations of the signal regions no matter how strong the signals are. Figure S1 (Supplementary Material) summarizes the simulation results when signal regions contain homogeneous signals and individual tests are independent, the case the M-SCAN method is ideally designed for. Different from the correlated case, as expected, M-SCAN performed better than the other procedures using all the four criteria. However, Q-SCAN with $\gamma = 1/4$ performed only slightly worse than M-SCAN. Figure S2 (Supplementary Material) summarizes the simulation results when the correlation matrix of individual tests is banded and signals are homogeneous. In this situation, the scaled Q-SCAN with $\gamma = 1/4$ and M-SCAN were the best two choices and their performances were similar.

Figure 2 summarizes the simulation results when signals are heterogeneous (Signal Structure 2) and the correlation matrix of individual tests is AR(1). In this situation, Q-SCAN with $\gamma = 1/4$ had a clear advantage in signal region detection over the other methods. The performance of Q-SCAN with $\gamma = 1/3$ was similar and slightly worse than that with $\gamma = 1/4$. Specifically, Q-SCAN with $\gamma = 1/4$ had a significantly lower dissimilarity measure and a higher $\kappa$ value than all the other methods. In addition, both Q-SCAN with $\gamma = 1/4$ and the unscaled quadratic scan procedure
had a better performance in terms of power and sensitivity compared to the other methods. Note that although the unscaled quadratic procedure had the highest power, its dissimilarity and kappa values were among the worst and did not decrease when the signal strength $\mu$ became larger, as observed in the homogeneous case. Figures S3 and S4 (Supplementary Material) summarize the simulation results with the same signal structure but individual tests are independent and have a banded correlation matrix respectively. Q-SCAN with $\gamma = 1/4$ performed the best. Compared to the homogeneous case, when signals had different directions in the signal region, M-SCAN lost power and also had difficulties in detecting the true locations of the signal regions.

Figure 3 summarizes the simulation results when signal SNPs are mixed with neutral SNPs in the signal regions (signal structure 3) and the correlation matrix of individual tests is AR(1). In this situation, Q-SCAN with $\gamma = 1/4$ performed better than the other procedures for signal region detection using all the four criteria. It had the highest power measured using signal points detection rate and sensitivity, the highest kappa value and the smallest dissimilarity measure than the other procedures. Q-SCAN with $\gamma = 1/3$ has a similar and a slightly worse performance than that with $\gamma = 1/4$. Figures S5 and S6 (Supplementary Material) summarize the simulation results with the same signal structure but the correlation matrix of individual tests is independent and banded, respectively. The results are similar to the AR(1) case and Q-SCAN with $\gamma = 1/4$ had a better performance than the other procedures for signal region detection.

In summary, our simulation study illustrates that Q-SCAN has an advantage in signal region identification over all the other methods, especially in the presence of signal variants of different directions, neutral variants or LD (correlation) among SNPs in signal regions. Based on our numerical studies, we recommend Q-SCAN with the scale parameter $\gamma = 1/4$ for GWAS signal region detection. We also did simulations when $C_n = 26$. The performance of the scaled Q-SCAN procedure with $\gamma < 1/2$ was quite robust to the choice of $C_n$ and choices of $\gamma$. The results for $C_n = 26$ could be found in the Supplementary Materials.

4.3 Power and Accuracy of Signal Region Detection Comparisons for Simulated GWAS Data

In order to compare the performance of the proposed Q-SCAN with M-SCAN and unscaled quadratic scan procedure in more realistic settings with more complex LD structures, we performed simulation studies on Chromosome 15 mimicking the lung cancer GWAS data to be analyzed in Section 5. Here the scan statistic of M-SCAN is the same as Section 4.2 which has adjusted for the
LD. Genotype data were generated in the same fashion as Section 4.1. The total sample sizes were also set as $M = 2000$, $M = 4000$ and $M = 8000$. We generated dichotomous phenotypes for case-control data under the logistic model

$$\text{logit}\{\mathbb{P}(Y = 1)\} = -2.2 + G_1\beta_1 + \cdots + G_s\beta_s, \quad m = 1, \cdots, M,$$

where $G_1, \cdots, G_s$ are the genotypes of the $s$ causal SNPs and $\beta_s$ are the log odds ratio for the causal SNPs. Case-control sampling was used and the numbers of cases and controls were equal. We considered three signal segments with each having a length 20. To mimic lung cancer GWAS data, we simulated four causal SNPs in each signal region, with each causal SNP having an effect size of $\beta = 0.18$. The two edges of each signal region were causal variants and the other causal SNPs were selected randomly within each signal region. We repeated the simulation 2000 times. Similarly, we used the same searching algorithm, and the Monte Carlo simulations based empirical threshold for controlling the family-wise error rate at the $\alpha_0 = 0.05$ level. We also used the same four criteria introduced in Section 4.2 to evaluate the performance of the proposed scan procedures.

Figure 4 summarizes the simulation results and the results are similar to those observed in Section 4.2. As the sample size increased, all the scan procedures performed better for signal region detection. Q-SCAN with $\gamma = 1/4$ had the best performance over the other methods. Q-SCAN with $\gamma = 1/3$ had a similar and slightly worse performance than that with $\gamma = 1/4$. Specifically, Q-SCAN with $\gamma = 1/4$ had a lower dissimilarity measure and a higher kappa value than the other methods. The difference was more appreciable as the sample size increased. Although the unscaled quadratic procedure had the best signal point detection rate and sensitivity, it had a worse similarity measure and kappa than Q-SCAN, indicating it did not provide accurate estimation of the locations of the signal segments. Q-SCAN with $\gamma = 1/4$ had the second best signal point detection rate and sensitivity, and the best dissimilarity measure and kappa value, indicating it performed well both in terms of power and accuracy in estimating the locations of signal segments. All the quadratic procedures performed better than the mean procedure M-SCAN. We also did simulations for some different effect sizes. The results were similar and could be found in the Supplementary Materials.

The computation time of Q-SCAN is linear in the number of variants in GWAS and the maximum searching window length and is hence computationally efficient. To analyze a sequence of 20000 variants, when we selected the maximum searching window length $C_n = 50$, the proposed Q-SCAN procedure took 6, 12 and 36 minutes for 2000, 4000 and 8000 individuals, respectively, on a 2.70GHz laptop with 12 Gb memory. Analyzing 1 million variants (the entire genome in GWAS)
on 2000 individuals requires 5 hours using the same laptop. The Q-SCAN procedure also works for parallel computing. Analyzing 1 million variants on 8000 individuals only requires 18 minutes if using 100 computation cores.

5 Application to the Lung Cancer GWAS Data

In this section, we analyzed the case-control lung cancer Genome-Wide Association Study conducted at the Massachusetts General Hospital. We were interested in detecting the genetic regions that were associated with the risk of non-small-cell lung cancer. The study genotyped 984 cases with non-small-cell lung cancer and 970 controls, all Caucasians, using the Illumina Human610-Quad BeadChip. A standard QC procedure was used. We analyzed 15519 common variants with Minor Allele Frequency >5% throughout Chromosome 15, using Q-SCAN with $\gamma = 1/4$.

We compared the performance of Q-SCAN with M-SCAN, and SKAT (Wu et al. 2011). The SKAT procedure was conducted for gene-level analysis, which pre-specifies analysis regions based on genes using SNPs within genes. It eliminates all the intergenic regions by removing all the SNPs in intergenic regions. Specifically, the gene-based SKAT test restricts analysis to 547 genes, which contain 9072 SNPs, i.e., it throws away 41.5% SNPs in chromosome 15. In contrast, the scan statistics Q-SCAN and M-SCAN scan the whole chromosome 15 continuously by using all the SNPs to identify signal regions.

For each SNP, we calculated the marginal test statistics $Z_i$ for the $i$th SNP by fitting a logistic regression model of case-control status on the genetic variant $i$, while controlling for age, sex, smoking status and top four principal components for population structure (Price et al. 2006). The sequence of individual SNP test statistics asymptotically follows a multivariate normal distribution. Their covariance matrix were estimated using equation (1).

After examining all the gene lengths and the linkage disequilibrium blocks, we set the largest searching window length $C_n = 50$. Specifically, there are 547 genes in Chromosome 15 and 93% of the genes have less than 50 SNPs. There are 3129 Haplotype blocks in Chromosome 15 and only one LD block has more than 50 SNPs. The LD blocks were calculated using Plink. Based on our simulation results, we chose $\gamma = 1/4$. We used an empirical threshold based on Monte Carlo simulations described in Section 4 to control for the family-wise error rate at the exact 0.05 level chromosome-15 wide.

For individual SNP analysis, only three SNPs rs578776, rs10151730 and rs8034191 had marginal $p$-values less than $10^{-4}$. They did not reach genome-wide significance after accounting for multiple
comparisons. However, the SNPs rs1051730 and rs8034191 in Chromosome 15 have been independently found to be associated with lung cancer risk in other studies (Hung et al. 2008; Amos et al. 2008).

We applied the proposed Q-SCAN with $\gamma = 1/4$ to this dataset to detect plausible genetic regions that are likely to be associated with lung cancer by scanning Chromosome 15 continuously. One significant SNP segment, which contains 46 SNPs, was detected by using the proposed scan procedure. The empirical family-wise error rate of this detected region was 0.023. The two formerly identified SNPs rs1051730 and rs8034191 based on individual SNP analysis that were associated with lung cancer risk (Hung et al. 2008; Amos et al. 2008) were contained in this estimated segment. The estimated signal segment can be used to determine the region for subsequent fine mapping.

M-SCAN did not detect any signal segment to reach chromosome-wide significance when we controlled for the family-wise error rate at 0.05. The most significant region detected by the Mean scan procedure contained 15 SNPs that included rs1051730 but missed rs8034191. The empirical family-wise error rate of this region was 0.0975. This indicates that our proposed procedure is more powerful than the Mean scan procedure for detecting signal regions in analyzing the lung cancer GWAS dataset.

For gene-level analysis using SKAT (Wu et al. 2011), only one gene CHRNA5 in Chromosome 15 was significant when the Bonferroni correction was applied to adjust for multiple testing for gene-level based analysis. The SKAT $p$-value of CHRNA5 was $7.44 \times 10^{-5}$, which corresponds to the Bonferroni-based family-wise error rate 0.04. CHRNA5 contained rs1051730, but not rs8034191 as this SNP is located out of genes. We also calculated the SKAT $p$-value for the estimated regions detected by Q-SCAN and M-SCAN. The $p$-value of these two detected regions were $3.71 \times 10^{-5}$ and $3.31 \times 10^{-4}$ respectively. This indicated that our procedure increased the power for detecting signal regions by estimating the locations of signal regions more accurately.

Figure 5 shows the Z-scores of individual SNPs in the estimated signal region detected by our proposed Q-SCAN and M-SCAN. It suggests that the SNP effects had different directions and were mixed with neutral variants in the signal region. These results explain why our Q-SCAN is more powerful than M-SCAN when applied to this dataset. We would also like to note that, the performance of our procedure is quite robust to the choice of the maximum searching length $C_n$ in the analysis of this dataset. When $C_n$ varied from 40 to 100, we obtained similar results as $C_n = 50$. Only one significant segment which contains SNPs rs1051730 and rs8034191 was detected using different choices of $C_n$, and the estimated signal region did not change when $C_n \geq 60$. 

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6 Discussions

In this paper, we propose a scaled quadratic scan (Q-SCAN) procedure to detect the existence and the locations of signal regions in GWAS. We show that the proposed scan procedure could control for the family-wise error rate using a proper threshold. Under regularity conditions, we also show that our procedure can consistently select the true signal segments and estimate their locations. Our simulation studies demonstrate that the proposed procedure has a better performance than the mean-based scan methods in the presence of SNP effects in different directions, or mixed signal SNPs and neutral SNPs in signal regions, and the correlation among variants in signal regions.

We derive a theoretical threshold to asymptotically control for the family-wise error rate. In practice, we recommend the use of an empirical threshold based on Monte Carlo simulations to control for the family-wise error rate at an exact $\alpha$—level. This step costs additional computation time when applying our procedure. Future research is needed to develop an analytic approximation to the significance level for the proposed scaled Q-SCAN statistics. We allow in this paper individual test statistics to be correlated, but assume stationary and $M_n$—dependence. This is a reasonable assumption in GWAS. It is of future research interest to extend our procedure to more general correlation structures. Moreover, the proposed scaled Q-SCAN procedure needs to specify a scale parameter $\gamma$. Our theoretical results show that Q-SCAN is consistent if $\gamma < 1/2$. Our simulation studies show that the results are robust to choices of $\gamma < 1/2$, with $\gamma = 1/4$ preferred for GWAS data. An interesting problem for future research is to develop a data-driven scale parameter estimation procedure.

A limitation of GWAS is that it only genotypes common variants. It has been found that common variants only explain a small fraction of heritability \cite{Manolio2009}. A vast majority of variants in the human genome are rare \cite{Tennessee2012}. A rapidly increasing number of Whole Genome Sequencing (WGS) association studies are being conducted to identify susceptible rare variants for human diseases and traits, for example the TopMed Program of the National Heart, Blood, Lung Institute (\url{http://www.nhlbi.nih.gov/research/resources/nhlbi-precision-medicine-initiative/topmed}) and the Genome Sequencing Program of the National Human Genome Research Institute (\url{http://gsp-hg.org/}). Region-based analysis is needed for rare variant analysis in WGS associated studies \cite{Wu2011, Lee2014}. It is of great interest to develop scan procedures for analysis WGS data to identify the regions associated with human diseases or traits.
We assume in this paper for GWAS, all the variants have the same weight in constructing the Q-SCAN statistic. In WGS association studies, upweighting rare variants and functional variants will boost power when most of causal variants are rare variants. It is of future research interest to extend our proposed scan procedure by weighting individual test statistics, e.g., using functional scores and minor allele frequencies of variants. We assume individual test statistics are asymptotically jointly normal. However, when most of variants are rare variants in the sequence, this normal assumption might not hold in finite samples especially for binary outcomes. An interesting problem of future research is to extend the results to the situation where individual test statistics are not normal and use the exact or approximated distributions of individual test statistics of rare variants.

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**Appendix**

Due to space limitation, we only present a sketch of the proofs here. The detailed proofs can be found in the attached Supplemental Materials.
Proof of Theorem 1

To prove Theorem 1 we first introduce the following two lemmas.

Lemma 1 Suppose that the centered stationary Gaussian process \( \{Z_j\}_{j \geq 1} \) has a spectral density function \( f(s) \in L_q(ds) \) for some \( 2 < q \leq \infty \). Let \( \theta \) satisfy \( 1/q < \theta < 1/2 \) and \( S_n = \sum_{j=1}^{n} (Z_j^2 - 1) \), we have

\[
\lim_{n \to \infty} n^{2\theta - 1} \log \left\{ \mathbb{P} \left( \frac{S_n}{n^{1/2}} \geq x \right) \right\} = -\frac{x^2}{2\sigma^2},
\]

where \( \sigma = \pi^{-1} \int_0^{2\pi} f^2(s) ds \).

Lemma 1 is the Large Deviation Principle for the quadratic additive functionals of centered stationary Gaussian processes. It follows directly from Theorem 3 in [Bryc and Dembo (1997)]. The following lemma shows the asymptotic property for the extreme value of a fixed length scan.

Lemma 2 Suppose that a centered stationary Gaussian process \( \{Z_j\}_{j \geq 1} \) has a spectral density function \( f(s) \in L_q(ds) \) for some \( 2 < q \leq \infty \). Assume \( \{Z_j\}_{j \geq 1} \) is \( M_n \)-dependent, where \( \log(M_n) = o(\log n) \). Let \( C_n \) be a sequence satisfying \( \lim_{n \to \infty} \log n/C_n^{1-2\theta} > 0 \) with \( 1/q < \theta < 1/2 \). Then we have

\[
\max_{0 \leq k \leq n-C_n} \frac{S_{k+C_n} - S_k}{\sqrt{2\sigma^2 C_n \log n}} \overset{P}{\to} 1,
\]

where \( \sigma^2 = \pi^{-1} \int_0^{2\pi} f^2(s) ds \).

Proof For any \( \eta > 0 \), we have

\[
\mathbb{P} \left\{ \left| \max_{0 \leq k \leq n-C_n} \frac{S_{k+C_n} - S_k}{\sqrt{2\sigma^2 C_n \log n}} - 1 \right| \geq \eta \right\} = \mathbb{P} \left\{ \max_{0 \leq k \leq n-C_n} \frac{S_{k+C_n} - S_k}{\sqrt{2\sigma^2 C_n \log n}} \geq 1 + \eta \right\} + \mathbb{P} \left\{ \max_{0 \leq k \leq n-C_n} \frac{S_{k+C_n} - S_k}{\sqrt{2\sigma^2 C_n \log n}} \leq 1 - \eta \right\} \triangleq K_1(\eta) + K_2(\eta).
\]

Let \( \alpha = \lim_{n \to \infty} \log n/C_n^{1-2\theta} \). We consider \( K_1(\eta) \) first, for \( n \) sufficiently large, by Lemma 1, we have

\[
K_1(\eta) = \mathbb{P} \left\{ \max_{0 \leq k \leq n-C_n} \frac{S_{k+C_n} - S_k}{\sqrt{2\sigma^2 C_n \log n}} > 1 + \eta \right\} \leq \sum_{k=0}^{n-C_n} \mathbb{P} \left\{ \frac{S_{k+C_n} - S_k}{\sqrt{2\sigma^2 C_n \log n}} \geq 1 + \eta \right\} \leq \exp \left\{ \log n - C_n^{1-2\theta} \alpha (1+\eta)^2 (1 + o(1)) \right\} = o(1).
\]

(A. 1)

Let \( A_k(\eta) = \{S_{k+C_n} - S_k > (1-\eta)\sqrt{2\sigma^2 C_n \log n}\} \), by Chung-Erdős inequality,

\[
K_2(\eta) = 1 - \mathbb{P} \left\{ \max_{0 \leq k \leq n-C_n} \frac{S_{k+C_n} - S_k}{\sqrt{2\sigma^2 C_n \log n}} > 1 - \eta \right\} = 1 - \mathbb{P} \left\{ \bigcup_{k=0}^{n-C_n} A_k(\eta) \right\} \leq 1 - \left[ \sum_{k=0}^{n-C_n} \mathbb{P} \{ A_k(\eta) \} \right]^2 \left[ \sum_{k=0}^{n-C_n} \mathbb{P} \{ A_k(\eta) \} + \sum_{i \neq j} \mathbb{P} \{ A_i(\eta) \cap A_j(\eta) \} \right].
\]
As \( \{Z_j\}_{j \geq 1} \) is \( M_n \)-dependent, \( A_i(\eta) \) is independent of \( A_j(\eta) \) when \( |i - j| > M_n + C_n \). We have

\[
\sum_{i \neq j} \mathbb{P}\{A_i(\eta) \cap A_j(\eta)\} = \sum_{|i-j| \leq M_n + C_n} \mathbb{P}\{A_i(\eta) \cap A_j(\eta)\} + \sum_{|i-j| > M_n + C_n} \mathbb{P}\{A_i(\eta) \cap A_j(\eta)\} \\
\leq n(M_n + C_n)\mathbb{P}\{A_0(\eta)\} + (n - C_n + 1)^2\mathbb{P}\{A_0(\eta)\}^2.
\]

Using similar discussion for \( (A.1) \), when \( n \) is sufficiently large, we have

\[
n\mathbb{P}\{A_0(\eta)\} = \exp\left[\log n\left\{1 - \frac{\alpha C_n^{1-2\theta}}{\log n} (1 - \eta)^2 (1 + o(1))\right\}\right] \geq n^\eta.
\]

Hence we get

\[
K_2(\eta) \leq \frac{n(M_n + C_n)\mathbb{P}\{A_0(\eta)\}}{n(M_n + C_n)\mathbb{P}\{A_0(\eta)\} + (n - C_n + 1)^2\mathbb{P}\{A_0(\eta)\}^2} \xrightarrow{n \to \infty} 0. \tag{A.2}
\]

Using \( (A.1) \) and \( (A.2) \), we have

\[
\mathbb{P}\left\{\max_{0 \leq k \leq n - C_n} \frac{S_{k+C_n} - S_k}{\sqrt{2\sigma^2 C_n \log n}} - 1 \geq \eta \right\} \to 0.
\]

For arbitrary \( \eta \), we complete the proof for Lemma 2. \(\square\)

Now we prove Theorem 1.

**Proof** For any \( \eta > 0 \),

\[
\mathbb{P}\left\{\max_{1 \leq i \leq C_n, i+j \leq n} \frac{S_{i+j} - S_i}{\sqrt{2\sigma^2 j^{2\gamma} C_n^{1-2\gamma} \log n}} - 1 \geq \eta \right\} = \mathbb{P}\left\{\max_{1 \leq i \leq C_n, i+j \leq n} \frac{S_{i+j} - S_i}{\sqrt{2\sigma^2 j^{2\gamma} C_n^{1-2\gamma} \log n}} \geq 1 + \eta \right\} \\
+ \mathbb{P}\left\{\max_{1 \leq i \leq C_n, i+j \leq n} \frac{S_{i+j} - S_i}{\sqrt{2\sigma^2 j^{2\gamma} C_n^{1-2\gamma} \log n}} \leq 1 - \eta \right\} \\
\triangleq A_1(\eta) + A_2(\eta).
\]

Note that

\[
\max_{1 \leq j \leq C_n, i+j \leq n} \frac{S_{i+j} - S_i}{\sqrt{2\sigma^2 j^{2\gamma} C_n^{1-2\gamma} \log n}} \geq \max_{0 \leq k \leq n - C_n} \frac{S_{k+C_n} - S_k}{\sqrt{2\sigma^2 C_n \log n}}.
\]

By Lemma 2 we have

\[
A_2(\eta) = \mathbb{P}\left\{\max_{1 \leq j \leq C_n, i+j \leq n} \frac{S_{i+j} - S_i}{\sqrt{2\sigma^2 j^{2\gamma} C_n^{1-2\gamma} \log n}} \leq 1 - \eta \right\} \\
\leq \mathbb{P}\left\{\max_{0 \leq k \leq n - C_n} \frac{S_{k+C_n} - S_k}{\sqrt{2\sigma^2 C_n \log n}} \leq 1 - \eta \right\} \xrightarrow{n \to \infty} 0. \tag{A.3}
\]

Next we consider \( A_1(\eta) \). Recall that \( \lambda_{ji} \) is the eigenvalue of \( \Sigma_j = (\sigma_{j_1, j_2})_{1 \leq j_1, j_2 \leq j} \) and \( \lambda_{C_n, \max} \) is the maximal eigenvalue of \( \Sigma_{C_n} \). Since \( f(\cdot) \in L_q \), we have \( \lambda_{C_n, \max} \leq (2\pi)^{-\frac{1}{\gamma}} C_n^{\frac{1}{\gamma}} ||f||_q \). Assume \( t_j =
\[ \sqrt{2(1 + \eta)^2 \log n / \{(1 + \eta/2)^2 \sigma^2 j^{2\gamma} C_n^{1-2\gamma}\}}, \quad j = 1, 2, \ldots, n, \] 
we have \( \lambda_{C_n, \text{max}} t_j \leq (2\pi)^{-\frac{1}{2}} ||f||_q C_n^{\gamma + \frac{1}{q} - \theta} = o(1) \) uniformly for \( j = 1, 2, \ldots, n \). Then for \( n \) sufficient large, by a Taylor expansion, we have

\[
A_1(\eta) = P\left\{ \max_{1 \leq j \leq C_n, i+j \leq n} \frac{S_{i+j} - S_i}{\sqrt{2\sigma^2 j^{2\gamma} C_n^{1-2\gamma} \log n}} \geq 1 + \eta \right\} \leq \sum_{j=1}^{C_n} P\left\{ S_j \geq (1 + \eta)\sqrt{2\sigma^2 j^{2\gamma} C_n^{1-2\gamma} \log nt_j} \right\}
\]

\[ \leq n \sum_{j=1}^{C_n} E\left\{ \exp(t_j S_j) \cdot \exp\left\{ -(1 + \eta)\sqrt{2\sigma^2 j^{2\gamma} C_n^{1-2\gamma} \log nt_j} \right\} \right\}
\]

\[ = \sum_{j=1}^{C_n} \exp\left\{ \log n - \frac{1}{2} \sum_{i=1}^{j} \log(1 - 2\lambda_{ji} t_j) - j t_j - (1 + \eta)\sqrt{2\sigma^2 j^{2\gamma} C_n^{1-2\gamma} \log nt_j} \right\}
\]

\[ \leq \sum_{j=1}^{C_n} \exp\left\{ \log n + (1 + \eta/2) j \sigma^2 t_j^2/2 - (1 + \eta)\sqrt{2\sigma^2 j^{2\gamma} C_n^{1-2\gamma} \log nt_j} \right\}
\]

\[ = \exp\left\{ \log n + \log C_n - \frac{(1 + \eta)^2 \log n}{1 + \eta/2} \right\} \xrightarrow{n \to \infty} 0. \quad (A. 4)
\]

Using (A. 3) and (A. 4), we have

\[ P\left\{ \max_{1 \leq j \leq C_n, i+j \leq n} \frac{S_{i+j} - S_i}{\sqrt{2\sigma^2 j^{2\gamma} C_n^{1-2\gamma} \log n}} - 1 \geq \eta \right\} \to 0.
\]

For arbitrary \( \eta \), we have \( Q_{\text{max}} / \sqrt{2\sigma^2 C_n^{1-2\gamma} \log n} \xrightarrow{p} 1 \). Thus we complete the proof of Theorem 1.

**Proof of Theorem 2**

To show the results for consistency of estimation of signal regions using the proposed method, we need the following lemma.

**Lemma 3 (Laurent and Massart (2000))** Let \( Y_1, \ldots, Y_D \) be i.i.d standard Gaussian variables. Let \( a_1, \ldots, a_D \) be nonnegative constants. We set

\[ ||a||_\infty = \sup_{1 \leq i \leq D} |a_i|, \quad ||a||_2^2 = \sum_{i=1}^{D} a_i^2.
\]

Let \( Z = \sum_{i=1}^{D} a_i(Y_i^2 - 1) \). Then, the following inequalities hold for any positive \( x \):

\[ P(Z \geq 2||a||_2 \sqrt{x} + 2||a||_\infty x) \leq \exp(-x), \quad P(Z \leq -2||a||_2 \sqrt{x}) \leq \exp(-x).
\]

Now we prove Theorem 2.
Proof As shown in Theorem 1 we have $\lambda_{p_n, \text{max}} = O(p_n^{\frac{1}{3}})$. Note that $\delta_n^2 \sqrt{\log n C_n^{1-2\gamma}} / \sqrt{C_n^{1-2\theta}} / \log n C_n^{\frac{1}{2}} \to \infty$ and $\text{Var}(\sum_{i \in I^*} Z_i^2) \leq 2p_n \sigma^2 + 4\lambda_{p_n, \text{max}} ||\mu_{I^*}||^2_2$, using Markov’s inequality,

$$\mathbb{P}\{Q(I^*) \leq h(n, C_n)\} = \mathbb{P}\{\sum_{i \in I^*} (Z_i^2 - 1) \leq h(n, C_n)p_n^{\gamma}\} \leq \frac{2p_n \sigma^2 + 4\lambda_{p_n, \text{max}} ||\mu_{I^*}||^2_2}{(||\mu_{I^*}||^2_2 - h(n, C_n)p_n^{\gamma})^2} = o(1).$$

Equation (8) follows. Next we prove (9) in Theorem 2. Denote by $J = \{I : |I| < L_n\}$, $J_1 = \{I \in J : I^* \subseteq I\}$, $J_2 = \{I \in J : |I| \geq |I^*|, I^* \not= \emptyset\}$ and $J_3 = \{I \in J : |I| < |I^*|\}$. Then,

$$\mathbb{P}\left[ \bigcup_{I \in J_1} \{Q(I) - Q(I^*) > 0\} \right] = \mathbb{P}\left[ \bigcup_{I \in J_1} \{Q(I) - Q(I^*) > 0\}\right] + \mathbb{P}\left[ \bigcup_{I \in J_2} \{Q(I) - Q(I^*) > 0\}\right] + \mathbb{P}\left[ \bigcup_{I \in J_3} \{Q(I) - Q(I^*) > 0\}\right].$$

We divide the remainder of the proof in three steps.

Step 1. $\mathbb{P}\left[ \bigcup_{I \in J_1} \{Q(I) - Q(I^*) > 0\}\right] \to 0.$

Assume $K_0 = \max\{h(n, C_n)p_n^{\gamma}, \sqrt{2\sigma^2 p_n (\log p_n)^2 \lambda_{p_n, \text{max}}}/2\}$,

$$\mathbb{P}\left[ \bigcup_{I \in J_1} \{Q(I) - Q(I^*) > 0\}\right] \leq \mathbb{P}\left[ \bigcup_{I \in J_1} \{\sum_{i \in I^*} (Z_i^2 - 1) - \frac{|I|}{|I^*|} K_0 > 0\}\right] + \mathbb{P}\left[ \sum_{i \in I^*} (Z_i^2 - 1) \leq K_0\right].$$

By the definition of $K_0$ and condition (B), the second part $\mathbb{P}\left[ \sum_{i \in I^*} (Z_i^2 - 1) \leq K_0\right] = o(1).$ For the first part,

$$\mathbb{P}\left[ \bigcup_{I \in J_1} \{\sum_{i \in I^*} (Z_i^2 - 1) - \frac{|I|}{|I^*|} K_0 > 0\}\right] \leq \sum_{k=1}^{C_n-p_n} 2p_n \mathbb{P}\left\{W_k - k > \{ (p_n + k)^{\gamma} - p_n^{\gamma}\} K_0/p_n^{\gamma}\right\},$$

where $W_k$ has same distribution as $\tilde{Z}^T \tilde{Z}$ with $\tilde{Z} \sim N(0, \Sigma_k)$ and $W_k$ is independent of $Z_i, i \in I^*.$

Let $\lambda_{k_i}$ be the eigenvalues of $\Sigma_k.$ When $p_n$ is bounded, by Lemma 3 for $n$ sufficiently large,

$$\sum_{k=1}^{C_n-p_n} 2p_n \mathbb{P}\left\{W_k - k > 2(\sum_{i=1}^{k} \lambda_{k_i}^{\gamma} (\log n)^{\frac{1}{2}} + 2\lambda_{k, \text{max}} \sqrt{\log n}) \right\} \leq \sum_{k=1}^{C_n-p_n} 2p_n \exp(-\sqrt{\log n}) + o(1) = o(1).$$

We next consider $p_n \to \infty.$ For $k \leq p_n,$ $\{ (p_n + k)^{\gamma} - p_n^{\gamma}\} K_0/p_n^{\gamma} \geq \sqrt{2\sigma^2 k (\log p_n)^2 \lambda_{\text{max}}}/2^{2\gamma}.$ Then, using Lemma 3,

$$\sum_{k=1}^{p_n} 2p_n \mathbb{P}\left\{W_k - k > \{ (p_n + k)^{\gamma} - p_n^{\gamma}\} K_0/p_n^{\gamma}\right\} \leq \sum_{k=1}^{p_n} 2p_n \exp(-3\log p_n) = o(1).$$

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For \(k > p_n\), \(\{(p_n + k)^\gamma - p_n^\gamma\}K_0/p_n^\gamma > \gamma \sqrt{2\sigma^2 C_n^{1-2\gamma} k^{2\gamma} \log n / 2^{1-\gamma}}\). Hence, by the same approach we discussed before, we could show that

\[
\sum_{k=p_n+1}^{C_n-p_n} 2p_n \mathbb{P}\left\{ W_k - k > \{(p_n + k)^\gamma - p_n^\gamma\}K_0/p_n^\gamma \right\} = o(1).
\]

This finishes the proof of Step 1.

**Step 2.** \(\mathbb{P}\left\{ \bigcup_{I \subseteq J_k} \{Q(I) - Q(I^*) > 0\} \right\} \rightarrow 0.\)

For any \(I \subseteq I^*\), by condition (C), \(||\mu_{I^*/I}||_2^2 = ||\mu_{I^*}||_2^2 - ||\mu_I||_2^2((|I^*| - |I|)||\mu_{I^*}||_2^2/2|I^*|).\) It follows that \(p_n \log(C_n)\lambda_{p_n, \max} = o(||\mu_{I^*}||_2^2).\) Assume \(I^* = (\tau_1^*, \tau_2^*),\) then there exists \(\epsilon_0 > 0\) satisfies that

\[
\inf_{\tau_1^* \leq i < \tau_2^*} \left\{ ||\mu_i, \tau_i^*||_2^2 / (3 + 2\sqrt{2})(2 \log(C_n)\lambda_{p_n, \max} + 2\sqrt{2}\sigma^2(\tau_2^* - \tau_1^*)) \log C_n \right\} \geq 1 + \epsilon_0,
\]

\[
\inf_{\tau_1^* \leq i < \tau_2^*} \left\{ ||\mu_i, \tau_i^*||_2^2 / (3 + 2\sqrt{2})(2 \log(C_n)\lambda_{p_n, \max} + 2\sqrt{2}\sigma^2(\tau_1^* - \tau_1^*)) \log C_n \right\} \geq 1 + \epsilon_0.
\]

Let \(A_1 = \bigcup_{k=1}^{p_n} \left\{ \sum_{i=1}^{k}(Z_{\tau_i^*+i}^2 - 1) > \sum_{i=1}^{k}(Z_{\tau_i^*+1-i}^2 - 1) > \sum_{i=1}^{k}(Z_{\tau_i^*+1-i}^2 - 1) \right\}\) and \(A_2 = \bigcup_{k=1}^{p_n} \left\{ \sum_{i=1}^{k}(Z_{\tau_i^*+1-i}^2 - 1) > \sum_{i=1}^{k}(Z_{\tau_i^*+1-i}^2 - 1) \right\}.\) Assume \(\nu_0 = (1 + \epsilon_0)(\sqrt{2\sigma^2 k \log C_n + 2\lambda_{p_n, \max} \log C_n}),\) by Lemma 3,

\[
\mathbb{P}(A_1) \leq \sum_{k=1}^{p_n} \mathbb{P}\left\{ \sum_{i=1}^{k}(Z_{\tau_i^*+1-i}^2 - 1) > \nu_0 \right\} + \mathbb{P}\left\{ \sum_{i=1}^{k}(Z_{\tau_i^*+i}^2 - 1) \leq \nu_0 \right\} = \sum_{k=1}^{p_n} \mathbb{P}\left\{ \sum_{i=1}^{k}(Z_{\tau_i^*+i}^2 - 1) \leq \nu_0 \right\} + o(1).
\]

Assume \(\Omega_k\) be the \(k \times k\) orthogonal matrix satisfies that \(\Omega_k \Sigma_k \Omega_k^T = \text{diag}(\lambda_{k1}, \ldots, \lambda_{kk}),\) where \(\lambda_{k1}, \ldots, \lambda_{kk}\) are the eigenvalues of \(\Sigma_k.\) Let \((\tilde{\mu}_{k1}, \ldots, \tilde{\mu}_{kk})^T = \Omega_k(\mu_{1}, \ldots, \mu_k)^T,\)

\[
\sum_{k=1}^{p_n} \mathbb{P}\left\{ \sum_{i=1}^{k}(Z_{\tau_i^*+1-i}^2 - 1) \leq \nu_0 \right\}
\]

\[
\leq \sum_{k=1}^{p_n} \mathbb{P}\left\{ \sum_{i=1}^{k}\lambda_{ki}\hat{Y}_{ki}^2 - 1 \leq -2(1 + \epsilon_0)(\sum_{i=1}^{k}\lambda_{ki}^2 \log C_n)^{1/2} \right\} + \mathbb{P}\left\{ 2 \sum_{i=1}^{k}\lambda_{ki}\hat{\mu}_{ki}Y_{ki} \leq (1 + \epsilon_0)\left( \sqrt{2\sigma^2 k \log C_n + 2(\sum_{i=1}^{k}\lambda_{ki}^2 \log C_n)^{1/2} + 2\lambda_{p_n, \max} \log C_n} - ||\mu_{(\tau_1^*, \tau_2^*)}||_2^2 \right) \right\},
\]

where \(Y_{ki} \sim N(0, 1)\) for \(i = 1, 2, \ldots, k\) and \(k = 1, 2, \ldots, p_n.\) By Lemma 3,

\[
\sum_{k=1}^{p_n} \mathbb{P}\left\{ \sum_{i=1}^{k}\lambda_{ki}^2 \hat{Y}_{ki}^2 - 1 \leq -2(1 + \epsilon_0)(\sum_{i=1}^{k}\lambda_{ki}^2 \log C_n)^{1/2} \right\} \leq \sum_{k=1}^{p_n} \exp\left\{ -(1 + \epsilon_0) \log C_n \right\} = o(1).
\]

Since \(\lambda_{ki}\hat{\mu}_{ki}Y_{ki} \sim N(0, \sum_{i=1}^{k}\lambda_{ki}^2 \hat{\mu}_{ki}^2),\) by Mills’ ratio, we could show that

\[
\sum_{k=1}^{p_n} \mathbb{P}\left\{ 2 \sum_{i=1}^{k}\lambda_{ki}\hat{\mu}_{ki}Y_{ki} \leq (1 + \epsilon_0)(2\sqrt{2\sigma^2 k \log C_n + 2\lambda_{p_n, \max} \log C_n} - ||\mu_{(\tau_1^*, \tau_2^*)}||_2^2 \right\} = o(1).
\]
Thus we have \( P(A_1) = o(1) \). Similarly, we also have \( P(A_2) = o(1) \). For any \( I \in J_2 \), we assume \( \tilde{I} = (\tau_1^* - |I^* \setminus I|, \gamma) \cdot (\tau_2^* + |I^* \setminus I|) \cdot 1(\tau_2^* \in I^* \setminus I) \), where \( 1(\cdot) \) is the indicator function. Let \( J_{21} = \{ I \in J_2 : |I| > |I^*| \} \),

\[
\mathbb{P}\left\{ \bigcup_{I \in J_{21}} \{ Q(I) - Q(I^*) > 0 \} \right\}
\]

\[
\leq \mathbb{P}\left\{ \bigcup_{I \in J_{21}} \left\{ \frac{1}{|I|^\gamma} \sum_{i \in I} (Z_i^2 - 1) - \frac{1}{|I^*|^\gamma} \sum_{i \in I^*} (Z_i^2 - 1) \right\} \cap A_1^c \cap A_2^c \right\} + \mathbb{P}(A_1) + \mathbb{P}(A_2)
\]

\[
\leq \mathbb{P}\left\{ \bigcup_{I \in J_{21}} \left\{ \frac{1}{|I|^\gamma} \sum_{i \in I} (Z_i^2 - 1) - \frac{1}{|I^*|^\gamma} \sum_{i \in I^*} (Z_i^2 - 1) \right\} \right\} + o(1).
\]

Using the same approach as that we discussed in Step 1, we have \( \mathbb{P}[\bigcup_{I \in J_{21}} |I|^\gamma \sum_{i \in I} (Z_i^2 - 1) > (|I^*|^\gamma - |I|^\gamma) \sum_{i \in I^*} (Z_i^2 - 1)] = o(1) \). Thus we complete the proof of Step 2.

**Step 3.** \( \mathbb{P}\left[ \bigcup_{I \in J_3} \{ Q(I) - Q(I^*) > 0 \} \right] \rightarrow 0. \)

Let \( \tilde{Z} = Z - \mu \). By condition (D) and condition (A), we could show that

\[
\mathbb{P}\left\{ \bigcup_{I \in J_3} \{ Q(I) - Q(I^*) > 0 \} \right\}
\]

\[
= \sum_{I \in J_3} \mathbb{P}\left\{ \left\{ \frac{1}{|I|^\gamma} \sum_{i \in I} (Z_i^2 - 1) - \frac{1}{|I^*|^\gamma} \sum_{i \in I^*} (Z_i^2 - 1) > 0 \right\} \right\}
\]

\[
+ \mathbb{P}\left\{ |I^*|^\gamma \sum_{i \in I^*} \tilde{Z}_i^2 > \frac{1}{5}(|I|^\gamma||\mu_{I^*}||_2^2 - |I^*|^\gamma||\mu_{I^* \cap \tilde{I}}||_2^2) \right\}
\]

\[
+ \mathbb{P}\left\{ 2(|I^*|^\gamma - |I|^\gamma) \sum_{i \in I^*} \mu_i \tilde{Z}_i > \frac{1}{5}(|I|^\gamma||\mu_{I^*}||_2^2 - |I^*|^\gamma||\mu_{I^* \cap \tilde{I}}||_2^2) \right\}
\]

\[
+ \mathbb{P}\left\{ -2|I|^\gamma \sum_{i \in I^\setminus \tilde{I}} \mu_i \tilde{Z}_i > \frac{1}{5}(|I|^\gamma||\mu_{I^*}||_2^2 - |I^*|^\gamma||\mu_{I^* \cap \tilde{I}}||_2^2) \right\}
\]

\[
\triangleq B_1 + B_2 + B_3 + B_4. \quad (A. 5)
\]

Here we only consider \( p_n \rightarrow \infty \). The proof of \( p_n \) is bounded is similar. Assume \( m_1 > 0 \) satisfies \( 1 - x^{1/\gamma} / (1 - x^\gamma) \geq m_1 \) for any \( x \in (0, 1) \). Then, by condition (C) and Lemma 3 for \( n \) sufficiently large,

\[
B_1 \leq \sum_{I \in J_3} \mathbb{P}\left\{ \sum_{i \in I \cap I^*} \tilde{Z}_i^2 > \frac{m_1 |I|^\gamma||\mu_{I^*}||_2^2}{( \log p_n )^{2 \gamma}} \right\} \leq \frac{2}{p_n} = o(1). \quad (A. 6)
\]

For \( B_2 \), using condition (C) and Lemma 3,

\[
B_2 \leq \sum_{I \in J_3} \mathbb{P}\left\{ \sum_{i \in I \cap I^*} \tilde{Z}_i^2 > 2 \sqrt{\sum_{i \in [I \cap I^*]} \lambda_i^2 |I \cap I^*|} \right\} \leq \frac{2}{p_n}. \quad (A. 7)
\]
For $B_3$, by condition (B) and condition (C), using Millos’ ratio, we could show that

$$B_3 \leq \sum_{I \in J_3} \mathbb{P}\left\{ \sum_{i \in I \cap I^*} \mu_i \hat{Z}_i / \sqrt{\mu_i^{T} \Sigma_{I \cap I^*} \mu_i} > \sqrt{m_1 |I| \gamma p_n^{1-\gamma} (\log p_n)^2 / 5} \right\} \leq \frac{1}{p_n}. \quad (A. 8)$$

Finally we consider $B_4$, by condition (D), we have $||\mu_{I^*\setminus I}||_2^2 \leq \sqrt{2|I^*\setminus I|/|I^*||\mu_{I^*}||_2^2}$. Then by condition (B) and Millos’ ratio, for $n$ sufficiently large, we could show that

$$B_4 \leq \sum_{I \in J_3} \mathbb{P}\left\{ \sum_{i \in I^* \setminus I} \mu_i \hat{Z}_i / \sqrt{\mu_i^{T} \Sigma_{I^* \setminus I} \mu_i} > \sqrt{8 \log p_n} \right\} \leq \frac{1}{p_n}. \quad (A. 9)$$

By (A. 5)-(A. 9),

$$\mathbb{P}\left\{ \bigcup_{I \in J_3} \{Q(I) - Q(I^*) > 0\} \right\} \leq \frac{6}{p_n} = o(1).$$

By combining Steps 1 to 3, we complete the proof. □

When there are multiple signal regions in the sequence, by Theorem 2, Q-SCAN could consistently detect all of them. Assume $I_1^*, \ldots, I_r^*$ are non-overlapping and well separated signal regions. Assume condition (A), (B) and (C) hold for all $I_j^*, j = 1, \ldots, r$. Then

$$\mathbb{P}_{H_1}(I_1^* \notin \hat{I}, \ldots, I_r^* \notin \hat{I}) \to 1.$$ 

Note that

$$\left\{ I_j^* \notin \hat{I} \right\} = \left\{ Q(I_j^*) \leq h(n, C_n) \right\} \cup \left\{ \max_{I \cap I_j^* \neq \emptyset, I \neq I^*_j} \{Q(I) - Q(I_j^*)\} > 0 \right\},$$

then

$$\mathbb{P}_{H_1}(I_j^* \notin \hat{I}) \leq \mathbb{P}_{H_1}\{Q(I_j^*) \leq h(n, C_n)\} + \mathbb{P}_{H_1}\left[ \max_{I \cap I_j^* \neq \emptyset, I \neq I^*_j} \{Q(I) - Q(I_j^*)\} > 0 \right].$$

Hence, by Theorem 2,

$$\mathbb{P}_{H_1}(I_1^* \notin \hat{I}, \ldots, I_r^* \notin \hat{I}) \geq 1 - \sum_{j=1}^{r} \mathbb{P}_{H_1}(I_j^* \notin \hat{I}) \geq 1 - \sum_{j=1}^{r} \left( \mathbb{P}_{H_1}\{Q(I_j^*) \leq h(n, C_n)\} + \mathbb{P}_{H_1}\left[ \max_{I \cap I_j^* \neq \emptyset, I \neq I^*_j} \{Q(I) - Q(I_j^*)\} > 0 \right] \right) = 1 - o(1).$$
Table 1: Simulation Studies of Family-Wise Error Rates. The family-wise error rate of the scaled quadratic scan procedure is estimated with 10000 simulated data set. In each data set, there are total number of $M = 2000$, $M = 4000$ or $M = 8000$ samples and the corresponding number of SNPs in the sequence are 15416, 15334 and 15450. The largest searching window length $C_n$ is set to 50. $Q-\gamma$ refer to the scan procedures using the scan statistics $\sum_{i\in I}(Z_i^2 - 1)/|I|^\gamma$. The 95% confidence interval of 10000 Bernoulli trials with probability 0.05 is [0.0457, 0.0543].

| Method | Continuous Phenotypes | Dichotomous Phenotypes |
|--------|-----------------------|------------------------|
|        | $M = 2000$ | $M = 4000$ | $M = 8000$ | $M = 2000$ | $M = 4000$ | $M = 8000$ |
| Q-1/2  | 0.0505    | 0.0517    | 0.0500    | 0.0483    | 0.0479    | 0.0525    |
| Q-1/3  | 0.0512    | 0.0505    | 0.0495    | 0.0486    | 0.0472    | 0.0513    |
| Q-1/4  | 0.0511    | 0.0508    | 0.0490    | 0.0484    | 0.0478    | 0.0510    |
| Q-0    | 0.0501    | 0.0514    | 0.0482    | 0.0490    | 0.0490    | 0.0513    |
Figure 1: Simulation study results for correlated SNPs with AR(1) correlation ($\rho = 0.6$) and Signal Structure 1 (Homogeneous Signals in the signal regions). The length of each true signal region is $p = 13$. All the SNPs have homogeneous signals with $\mu_i = \mu$ ($i = 1, \cdots, 13$). The largest searching window length is $C_n = 39$. 2000 simulated data sets were generated and we generated $n = 10000$ individual test statistics for each simulated data set. Q-$\gamma$ and Mean refer to the scan procedures using the scan statistics $\sum_{i \in I}(Z_i^2 - 1)/|I|$ and $|\sum_{i \in I}Z_i|/\sqrt{\text{var}(\sum_{i \in I}Z_i)}$, respectively.
Figure 2: Simulation study results for correlated SNPs with AR(1) correlation ($\rho = 0.6$) and Signal Structure 2 (Heterogeneous Signals in the signal regions). The length of each true signal region is $p = 13$. All the SNPs have the same signal strength but in different directions: $\mu_i = \mu$ if $i \neq 3, 7, 11$ and $\mu_i = -\mu$ if $i = 3, 7, 11$. The largest searching window length is $C_n = 39$. 2000 simulated data sets were generated and we generated $n = 10000$ individual test statistics for each simulated data set. $Q-\gamma$ and Mean refer to the scan procedures using the scan statistics $\sum_{i \in I} (Z_i^2 - 1)/|I|^{\gamma}$ and $|\sum_{i \in I} Z_i|/\sqrt{\text{var}(\sum_{i \in I} Z_i)}$, respectively.
Figure 3: Simulation study results for correlated SNPs with AR(1) correlation ($\rho = 0.6$) and Signal Structure 3 (Mixed signal and neutral SNPs in the signal regions). The length of each true signal region is $p = 13$ and signal SNPs are mixed with neutral SNPs in the signal regions with $\mu_i = \mu$ when $i = 1, 5, 9, 13$, $\mu_i = -\mu$ when $i = 3, 7, 11$ and $\mu_i = 0$ if $i$ is an even position ($i = 1, \ldots, 13$). 2000 simulated data sets were generated and we generated $n = 10000$ individual test statistics for each simulated data set. The largest searching window length is $C_n = 39$. Q-$\gamma$ and Mean refer to the scan procedures using the scan statistics $\sum_{i \in I} (Z_i^2 - 1) / |I|$ and $|\sum_{i \in I} Z_i| / \sqrt{\text{var}(\sum_{i \in I} Z_i)}$, respectively.
Figure 4: Power and accuracy of estimated signal region comparisons of Q-SCAN and M-SCAN on Chromosome 15. For total sample size $M = 2000$, $M = 4000$ and $M = 8000$, the sequence contains 15416, 15334 and 15450 SNPs, respectively. The maximum searching window length $C_n = 50$. The length of each true signal region is $p = 20$ and each signal region contains 4 randomly selected causal SNPs with effect size 0.18. We repeated the simulation for 2000 times. $Q_{-\gamma}$ and Mean refer to the scan procedures using the scan statistics $\frac{\sum_{i \in I}(Z_i^2 - 1)}{|I|^\gamma}$ and $\frac{|\sum_{i \in I} Z_i|}{\sqrt{\text{var}(\sum_{i \in I} Z_i)}}$, respectively.
Figure 5: Z-scores of individual SNP analysis in the estimated signal region of chromosome 15 of the MGH lung cancer GWAS data. The signal region was estimated using the proposed Q-SCAN with $\gamma = 1/4$. The region between two blue lines is the estimated signal region detected by the M-SCAN. The two red dots are SNPs rs1051730 and rs8034191 which are the SNPs associated with lung cancer that were identified in published GWAS.