Association screening of common and rare genetic variants by penalized regression

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ABSTRACT

Motivation: This article extends our recent research on penalized estimation methods in genome-wide association studies to the realm of rare variants.

Results: The new strategy is tested on both simulated and real data. Our findings on breast cancer data replicate previous results and shed light on variant effects within genes.

Availability: Rare variant discovery by group penalized regression is now implemented in the free program Mendel at http://www.genetics.ucla.edu/software/

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Supplementary information: Supplementary data are available at Bioinformatics online.

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1 INTRODUCTION

Genome-wide association studies (GWASs) have enjoyed varying degrees of success in the past decade (Easton and Eccles, 2008; Frazer et al., 2009; Lettre and Rioux, 2008). The failure of single nucleotide polymorphism (SNP)-based studies to explain a substantial fraction of trait variation is hardly surprising given the tendency of selection to drive even weakly deleterious mutations to extinction. There are several candidates for the missing dark matter of genetic epidemiology. Among these are: (i) copy number variants (CNVs); (ii) polygenes of small effect; (iii) interactions between genes and between genes and environment; (iv) epigenetic effects; and (v) rare variants. Rare variants are currently attracting the most attention. CNVs are subject to the same selective forces as SNPs. The sole benefit of discovering polygenes of small effect is the insight these provide into biochemical pathways and genetic networks. Detecting interactions is problematic unless they are large or sample sizes are very large. Epigenetic effects and parent-of-origin effects are clearly important in certain settings and deserve more study. In view of the recent striking advances in large-scale sequencing (Hodges et al., 2007), the search for rare variants is apt to be the most promising route to disease gene discovery.

Statistical methods must evolve to meet the challenges of sequence data. Most current analysis methods are predicated on the common disease common variant (CDCV) hypothesis, which postulates that common diseases are caused by common variants of small to modest effect. The competing common disease rare variant (CDRV) hypothesis postulates that common diseases are caused collectively by multiple rare variants of moderate to large effect. Macular degeneration is cited as an example supporting the CDRV hypothesis (RetNet, 2010). Because macular degeneration onset is typically late in life, it has a small impact on Darwinian fitness. The CDRV hypothesis receives support from traits such as low plasma levels of HDL cholesterol (Cohen et al., 2004), cystic fibrosis (Dean and Santis, 1994), colorectal adenomas (Azzopardi et al., 2008), familial breast cancer (Johnson et al., 2007) and schizophrenia (Walsh et al., 2008). The distinction between the two hypotheses is less sharp than proponents might suggest in the heat of argument. There is a spectrum of deleterious allele frequencies within many disease genes, and special circumstances of human history may favor one hypothesis over the other, depending on the diseases and populations studied (Nielsen et al., 2007, 2009).

It makes good statistical sense to consider all predictors (SNP variants and environmental covariates) in concert. Because rare disease predisposing alleles may be present in only a handful of patients, the traditional variant-by-variant approach is doomed to low power. A remedy is to group variants by gene or pathway membership. Once this is done, the strongest marginal signal is assessed by a weighted sum test (Madsen and Browning, 2009) or by a groupwise test exploiting the multivariate and collapsing strategies of Li and Leal (2008). Multiple testing remains a major concern.

The current article extends our recent research on penalized estimation methods in GWAS (Wu et al., 2009) to the realm of rare variants. This approach to association mapping has several advantages: (i) it applies to both ordinary and logistic regression; (ii) it is parsimonious and very fast; (iii) it offers a principled approach to model selection when the number of predictors exceeds the number of study participants; and (iv) it handles interactions gracefully. Our current software relies on lasso penalties and forms part of the Mendel package (Lange et al., 2001). Here, we discuss how to incorporate group penalties that make it easier for related predictors to enter a model once one of the predictors does. For example, one could group all SNPs within a single gene or within several genes in the same pathway. We will argue that a mixture of group penalties and single-predictor penalties tends to work best in practice and constitutes a good alternative to forced collapsing.

When we pass to penalized estimation, model selection is emphasized over hypothesis testing. The lasso penalty is one of

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they reappear in replication, but in a more benign form because the coefficients, $\|\beta\|_2$ represents the loss function minimized in ordinary least squares; the $\ell_1$ contribution $|\beta_j|$ is the lasso penalty function. Its multiplier $\lambda > 0$ is the penalty constant. The lasso shrinks the estimates of the regression coefficients $\hat{\beta}_j$ toward 0. An alternative ridge penalty $\lambda\|\beta\|_2^2$ also shrinks parameter estimates, but it is not effective in reducing the vast majority of them to 0. For this reason the lasso penalty is preferred to the ridge penalty. Both lasso and ridge regressions are special cases of the bridge regression (Fan, 1999). The constant $\lambda$ can be tuned to give any desired number of predictors. In this sense, lasso-penalized regression performs continuous model selection. The order predictors enter a model as $\lambda$ decreases is roughly determined by their impact on the response. Exceptions to this rule occur for correlated predictors. Logistic regression is handled in a similar manner. Instead of equating the loss function to a sum of squares, we equate it to the negative loglikelihood. The loglikelihood itself can be written as

$$L(\theta) = \sum_{i=1}^{n} \left[ y_i \log(\mu_i) + (1 - y_i) \log(1 - \mu_i) \right],$$

where $n$ is the number of responses, $\theta = (\mu, \beta)$ the parameter vector and the success probability $\mu_i$ for trial $i$ is defined by

$$\mu_i = \frac{e^{\beta_0 + \sum_{j=1}^{p} \beta_j x_{ij}}}{1 + e^{\beta_0 + \sum_{j=1}^{p} \beta_j x_{ij}}},$$

with $x_{ij}$ the $i$th row of the design matrix $X$ and $\mu$ an intercept parameter. In practice, statisticians also include the intercept in the ordinary regression model. It can be accommodated by taking the first column of $X$ to be the vector 1 whose entries are identically 1. Because the intercept is felt to belong to any reasonable model, the lasso and ridge penalties omit it. To put the regression coefficients on an equal footing, all predictors should be centered around 0 and scaled to have approximate variance 1. There is a parallel development of lasso-penalized regression for generalized linear models (Park and Hastie, 2007).

In each case, the objective function is written as

$$f(\hat{\beta}) = L(\theta) - \lambda \|\beta\|_1$$

as the difference between the loglikelihood and the lasso penalty. Because we now maximize $f(\beta)$, we subtract the penalty.

In some applications, it is natural to group predictors (Yuan and Lin, 2006). This raises the question of how to penalize a group of parameters. The lasso penalty and the ridge penalties separate parameters. If a parameter enters a model, then it does not strongly inhibit or encourage other associated parameters entering the model. Euclidean penalties have a more subtle effect.

The remainder of the article is organized as follows. Section 2 describes our statistical approach and optimization algorithms. It introduces the lasso and group Euclidean penalties, and shows how they can be implemented in linear and logistic regression. The coordinate descent algorithms covered are exceptionally quick and permit optimal tuning of the penalty constant by cross-validation. Section 2 also presents an efficient method for simulating samples under the CDRV model. Section 3 applies the mixed penalty method to two simulation examples. Section 4 analyzes a breast cancer dataset that is small enough to allow comparison to traditional model selection. The discussion highlights some strengths and weaknesses of model selection with mixed penalties and suggests potentially helpful extensions.

2 METHODS

2.1 Lasso and group-penalized regression

The lasso-penalized linear regression (Donoho, 1994; Tibshirani, 1996; Wu and Lange, 2008) is applied to high-dimensional regression problems with tens to hundreds of thousands of predictors. Estimates are derived by minimizing

$$f(\beta) = \frac{1}{2} y - X\beta \|_{\ell_2}^2 + \lambda \|\beta\|_1,$$

where $y$ is the response vector, $X$ the design matrix, $\beta$ the vector of regression coefficients, $\|\cdot\|_1 = \sum_j |\beta_j|$ the Euclidean ($\ell_1$) norm and $\|\cdot\|_2$ the taxicab ($\ell_2$) norm. The sum of squares $|y - X\beta|_{\ell_2}^2$ represents the loss function minimized in ordinary least squares; the $\ell_1$ contribution $|\beta_j|$ is the lasso penalty function. Its multiplier $\lambda > 0$ is the penalty constant. The lasso shrinks the estimates of the regression coefficients $\hat{\beta}_j$ toward 0. An alternative ridge penalty $\lambda\|\beta\|_2^2$ also shrinks parameter estimates, but it is not effective in reducing the vast majority of them to 0. For this reason the lasso penalty is preferred to the ridge penalty. Both lasso and ridge regressions are special cases of the bridge regression (Fan, 1999). The constant $\lambda$ can be tuned to give any desired number of predictors. In this sense, lasso-penalized regression performs continuous model selection. The order predictors enter a model as $\lambda$ decreases is roughly determined by their impact on the response. Exceptions to this rule occur for correlated predictors. Logistic regression is handled in a similar manner. Instead of equating the loss function to a sum of squares, we equate it to the negative loglikelihood. The loglikelihood itself can be written as

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In some applications, it is natural to group predictors (Yuan and Lin, 2006). This raises the question of how to penalize a group of parameters. The lasso penalty and the ridge penalties separate parameters. If a parameter enters a model, then it does not strongly inhibit or encourage other associated parameters entering the model. Euclidean penalties have a more subtle effect. Suppose $G$ denotes a group of parameters. Consider the objective function

$$f(\hat{\beta}) = L(\theta) - \lambda \|\beta\|_1$$

with a Euclidean penalty on each group. Here, $\mathbf{G}_k$ is the subvector of the regression coefficients corresponding to group $G$. In coordinate ascent, we increase $f(\beta)$ by moving one parameter at a time. If a slope parameter $\beta_j$ is parked at 0, when we seek to update it, its potential to move off 0 is determined by the balance between the increase in the loglikelihood and the decrease in the penalty. The directional derivatives of these two functions measure these two opposing forces. The directional derivative of $L(\hat{\beta})$ is the score $\frac{d}{d\beta_j} L(\hat{\beta})$ for movement to the right and the negative score $-\frac{d}{d\beta_j} L(\hat{\beta})$ for movement to the left. An easy calculation shows that the directional derivative of $\lambda(\mathbf{G}_k)\|\beta\|_2$ is $\lambda$ in either direction at $\beta_j = 0$ when $\beta_j = 0$ for all $i \in G$ with $i \neq j$. In this case we note that $\|\beta\|_2^2 = \|\mathbf{G}_k\|_2$. If $\beta_j \neq 0$, then the partial derivative of $\lambda(\mathbf{G}_k)\|\beta\|_2$ with respect to $\beta_j$ is $\mathbf{G}_k \beta_j / \|\mathbf{G}_k\|_2$. Hence, the directional derivatives both vanish at $\beta_j = 0$. In other words, the local penalty around 0 for each member of a group relaxes as soon as the regression coefficient for one member moves off 0. Euclidean group penalties run the risk of selecting response-neutral predictors. As soon as one predictor from a group enters a model, it opens the door for other predictors from the group to enter the model. For this reason,
we favor a mixture of group and lasso penalties in ordinary regression. In our genetics context, lasso penalties keep the pressure on to ensure for neutral mutations to be excluded, even if they occur in causative genes or pathways. There is no need to group SNPs that occur outside coding or obvious regulatory regions. However, it seems reasonable in the absence of other knowledge to penalize all SNPs equally. This suggests that all Euclidian penalties have the same scale and that the sum of the group and lasso scales for each SNP be the same. Thus, if SNP \( j \) belongs to group \( G \), it should experience penalty \( \lambda_G |\beta_j|_2 + \lambda_k |\beta_j| \). If it belongs to no group, it should experience penalty \( \lambda_k |\beta_j| \) with \( \lambda = \lambda_k + \lambda_G \).

Imposition of lasso and Euclidian penalties has further advantages. In addition to enforcing model parsimony and selecting relevant parameters, both penalties improve the convergence rate in minimizing the objective function. Because the penalties are convex, they also increase the chances for a unique minimum point when the loss function is non-convex. As we see, both kinds of penalties are compatible with coordinate descent, which is by far the fastest optimization method in sparse regression.

### 2.2 Algorithms

Coordinate descent/ascent has proved to be an extremely efficient algorithm for fitting penalized models in high-dimensional problems (Friedman et al., 2007; Wu and Lange, 2008; Wu et al., 2009). Traditional algorithms such as Newton’s method and scoring are not computationally competitive. Cyclic coordinate descent/ascent optimizes the objective function one parameter at a time, fixing the remaining parameters. Block relaxation generalizes cyclic coordinate descent by cycling through disjoint blocks of parameters and updating one block at a time. Meier et al. (2008) use block relaxation to fit logistic regression. The extreme efficiency of cyclic coordinate descent/ascent in high-dimensional problems stems from the low cost of the univariate updates and the fact that most parameters never budge from their initial value of 0. Here, we present cyclic coordinate descent for linear and logistic regression with mixed lasso and group penalties.

#### 2.2.1 Logistic regression with cases and controls

The lack of continuity of the first partial derivative at the point \( \beta_j = 0 \) does not prevent the directional derivatives from being well defined. The Newton’s update of \( \beta_j \)

\[
\beta_j^{(n+1)} = \beta_j^{(n)} - \frac{\partial^2}{\partial \beta_j^2} f^{(n)}(\beta_j^{(n)})^{-1} \frac{\partial f}{\partial \beta_j}(\beta_j^{(n)})
\]

almost always converges within five iterations. At each iteration one should check that the objective function is driven uphill. If the ascent property fails, then the simple remedy of step halving is available.

#### 2.2.2 Ordinary regression with a quantitative trait

The objective function to be minimized is

\[
f(\beta) = \frac{1}{2} \sum_{i=1}^{n} (y_i - \mu - X\beta)^2 + \lambda G |\beta|_2 + \lambda_k |\beta|.
\]

The Newton update of the intercept is the obvious average

\[
\mu^{(n+1)} = \frac{1}{n} \sum_{i=1}^{n} x_i y_i.
\]

To implement Newton’s method for a slope parameter \( \beta_j \) belonging to group \( G \), one employs the first and second partial derivatives

\[
\frac{\partial}{\partial \beta_j} f(\beta) = \sum_{i=1}^{n} x_i y_i - \sum_{i=1}^{n} x_i (1-p_i) (\beta_j)\text{sgn}(\beta_j),
\]

\[
\frac{\partial^2}{\partial \beta_j^2} f(\beta) = \sum_{i=1}^{n} x_i^2 - \sum_{i=1}^{n} (x_i (1-p_i))^2 (\beta_j^2)\text{sgn}(\beta_j).
\]

With these derivatives in place, the 1D Newton’s update (3) is pertinent. Once again iteration is confined to the left or right half-axis, whichever shows promise. Because the objective function is concave, the two directional derivatives cannot be simultaneously positive. If \( \beta_j \) belongs to group \( G \), then the two first two partial derivatives are

\[
\frac{\partial}{\partial \beta_j} f(\beta) = \sum_{i=1}^{n} x_i y_i - \sum_{i=1}^{n} x_i (1-p_i) (\beta_j)\text{sgn}(\beta_j),
\]

\[
\frac{\partial^2}{\partial \beta_j^2} f(\beta) = \sum_{i=1}^{n} x_i^2 - \sum_{i=1}^{n} (x_i (1-p_i))^2 (\beta_j^2)\text{sgn}(\beta_j).
\]
Algorithm 1. Given MAFs $p_1, \ldots, p_n$ and variant specific penetrances $f_{ij}$ for $i = 1, \ldots, v$ and $j = 0, 1, 2$, simulate $D$ cases and $N$ controls.

1. Calculate genotype frequencies under HWE: $Pr(G_i = j)$
2. Calculate variant prevalences $h_i = \sum_j Pr(G_i = j)f_{ij}$
3. Calculate the lower triangular probability table $Q(0.0, v, v) \vdash via recursion $Q(0.0, 0) = 1$
   \[
   Q(0.1, 0) = \frac{1}{k}Q(0.1, 0) = \frac{1}{k}Q(0.1, 0) + (1 - \frac{1}{k})Q(0.1, 1)
   \]
   for each control do
   Sample from $Pr(G_i = j | I_i = 0) = (1 - f_{ij})/(1 - k)$ for $i = 1, \ldots, v$
   end for
   for each case do
   Sample from $Pr(G_i = j | I_i = 1) = f_{ij}$ for $i = 1, \ldots, v$
   Sample $I_i$ from Bernoulli with parameter $\hat{Q}(m - 1.5S - 1)/Q(m, S)$
   Sample $G_i$ from $Pr(G_i | I_i)$
   $S = S - I_i$
   end for

3. ANALYSIS OF SIMULATED DATA

Our first simulation example compares mixed group and lasso penalties to pure lasso and pure group penalties in association testing. Figure 1 shows the solution paths of a simulation example with 500 cases and 500 controls at various mixtures of lasso and group penalties for three genes. Gene 1 (red) contains one common causal variant [minor allele frequency (MAF) 10%] and RR 1.2] and four neutral rare variants. Gene 2 (green) contains five causal rare variants (MAF 1% and RR 5) and five neutral rare variants. Gene 3 (blue) contains 10 neutral rare variants. All neutral rare variants have MAF 1% and RR 1. The wild-type penetrance $f_{00}$ is set at 0.01. The pure lasso penalty ($\lambda_1/\lambda_2 = 1$) picks up significant variants (common and rare) sequentially. The pure group penalty ($\lambda_2/\lambda_3 = 0$) picks up groups (genes) 1, 2 and 3 sequentially. The mixed group plus lasso penalty ($\lambda_2/\lambda_3 = 0.75$ or 0.50) achieves a good compromise between the two.

Our second simulation example involves 100 simulations each with 500 controls and 500 cases under different scenarios, reflecting heterogeneity in both MAFs and RRs. There are 10 participating genes, each with 5 rare variants. Across the simulations, the MAF is uniformly distributed from 0.1% to 1%. For $i = 1, \ldots, 5$, gene has $i$ causal rare variants. Therefore, the model has 15 causal rare variants dispersed over 5 genes and 35 neutral rare variants dispersed over 10 genes. All neutral variants have RR 1. The wild-type penetrance $f_{00}$ is set at 0.01. Figure 2 reports the receiver operating characteristic (ROC) curves calculated from selected variants and genes, with the proportion of the lasso penalty $\lambda_2/\lambda_3$ set at 0 (pure group penalty), 0.5 and 1.0 (pure lasso penalty). Each point of the ROC curves records the true and false positive rates of the selected variants (first row) or genes (second row) at a specific $A$ value. Inspection of these graphs shows that the performance of the mixed group and lasso penalties dominates that of the pure lasso penalty in variant selection. Note how the green ROC curves are shifted toward the upper left. The effects on gene selection is not clear-cut. The second and third scenarios (columns) support our contention that penalized regression with mixed penalties performs better when any of the causal variants is relatively common or has a high RR in groups.

4. APPLICATION TO FAMILY CANCER REGISTRY DATA

Germline mutations in genes from various DNA repair pathways, most notably BRCA1, BRCA2 and ATM, have been shown to dramatically increase the risk of familial breast cancer but do not explain all of the risk (Claus et al., 1996; Ford et al., 1994; Gatti, 1998; Wooster et al., 1995). Based on a candidate gene study of the double-strand break repair (DSBR) pathway, we have identified SNPs from genes involved in DSBR (XRCC4, XRCC2, NBS1, RAD21, TP53, BRIP1, ZNF350) that are associated with risk of familial breast cancer in single SNP analyses (Sehl et al., 2009). Identifying group effects from this pathway can be helpful in understanding factors that modulate an individual’s risk of developing breast cancer. We wish to identify group effects by gene and apply here mixed group and lasso-penalized regression.
Penalized regression for GWAS

Fig. 1. A simulation example with 500 cases and 500 controls. There are three genes. Gene 1 (red) contains one common causal variant (MAF 10% and RR 1.2) and four neutral rare variants. Gene 2 (green) contains five causal rare variants (MAF 1% and RR 5) and five neutral rare variants. Gene 3 (blue) contains 10 neutral rare variants. All neutral rare variants have MAF 1% and RR 1. The wild-type penetrance $f_0$ is set at 0.01. The pure lasso penalty ($\lambda_L/\lambda = 1$) picks up significant variants (common and rare) sequentially. The pure group penalty ($\lambda_L/\lambda = 0$) picks up the genes (groups) 1, 2 and 3 sequentially. The mixed group plus lasso penalty ($\lambda_L/\lambda = 0.75$ or 0.50) achieves a good compromise between the two.

Fig. 2. ROC curves based on 100 simulations each with 500 controls and 500 cases. The first row is for variants and the second row for genes. MAFs of all variants are uniform between 0.1% and 1%. Neutral variants have RR 1. Column 1: RRs of causal variants are uniform between 1.2 and 5. Column 2: RRs of causal variants are uniform between 1.1 and 2, except one RR is set to 10 in each causal gene. Column 3: MAF of one variant is set to 5% in each causal gene. The true positive rate (sensitivity) is the proportion of causal variants/genes correctly identified, while the false positive rate (1-specificity) is the proportion of neutral variants/genes identified as causal.
Fig. 3. SNPs and genes from the DSBR pathway selected by group lasso penalized regression based on familial breast cancer data. All results assume an additive model. Panels reveal the varying trajectories of SNP and gene entrances into the model under varying proportions of lasso to total (lasso plus group) penalty.

Family Cancer Registry: data are taken from genotype samples of participants enrolled in the UCLA Family Cancer registry. To be eligible, individuals must have a personal or family history of either a known cancer genetic susceptibility, such as a mutation in BRCA1 or BRCA2, or a family history containing at least two first or second degree relatives who are afflicted with the same primary cancer. This enriched sample of participants allows for the identification of factors that modulate risk of breast cancer. Data analysis has to be fairly subtle because of the way in which the participants were enrolled.

Analysis: we performed penalized logistic regression with the dependent variable, breast cancer status (affected versus unaffected) coded as a binary outcome. We limited our sample to 399 Caucasian participants because other ethnic groups were too small to fully characterize and provide little power to detect differences. There were 196 affected and 203 unaffected individuals. Age was used as a covariate in our analysis. The well-known association of age with breast cancer was confirmed in our previous analysis (Sehl et al., 2009). We imputed missing data for covariates using the mean value for continuous variables and the most frequent category for categorical variables.

SNPs were excluded from our analysis if genotype call rates were <75%. Missing SNPs were imputed using the SNP imputation option of the Mendel 10.0 software (Lange et al., 2001). 148 SNPs from the DSBR pathway were grouped by gene. These 17 genes included BRCA1, BRCA2, BRIP1, ATM, RAD50, RAD51, RAD52, RAD54L, RAD21, TP53, NBS1, XRCC2, XRCC4, XRCC5, MRE11A, ZNF350 and LIG4. Some genes carried large numbers of SNPs (e.g. BRCA2 had 19 SNPs), and some genes had only one SNP for analysis. SNPs were analyzed under additive models. Penalized regression was performed under varying proportions of lasso and group penalties. Analysis under a dominant model leads to similar conclusions (data not shown).

Results: although most of the SNPs in this dataset are common, 4 have MAFs <1%, 5 have MAF between 1% and 5% and 13 have MAF between 5% and 10%. Figure 3 plots the selection trajectories for groups of SNPs and demonstrate the ability of mixed group and lasso-penalized regression to select SNPs within a gene as a group. As the total penalty grows, SNPs are selected either singly or as groups. In the case of the pure lasso, SNPs enter the model singly, and in the case of the pure group penalty, genes enter the model with their full sets of SNPs. In the mixed cases, we see that either single SNPs or sets of SNPs grouped by gene enter the model. When a group enters in the mixed cases, it need not contain all of the SNPs in that gene.

Age was the first predictor selected in all models as expected. The content and order of selection of the top four gene-defined groups under varying proportions of lasso to total penalty are shown in Table 1. Under a purely lasso penalty, single SNPs from genes BRIP1, RAD21, RAD52 and XRCC4 are selected. As we increase the proportion of the group penalty, more SNPs from each of these four genes are selected together as a group.

It is reassuring that a broad range of proportions (0.25–0.75) of the lasso penalty deliver stable results. In most models, the same 3 SNPs from RAD21, and the same 4–5 SNPs from XRCC4 are selected. The 3 SNPs from RAD21 lie in a common haplotype block as defined by...
Table 1. Top four groups of SNPs selected under varying lasso and group penalties and an additive model

<table>
<thead>
<tr>
<th>(\lambda_i/k)</th>
<th>Second</th>
<th>Third</th>
<th>Fourth</th>
<th>Fifth</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BRIP1</td>
<td>XRC4C</td>
<td>RAD21</td>
<td>RAD52</td>
</tr>
<tr>
<td>0.75</td>
<td>RAD21</td>
<td>XRC4C</td>
<td>BRIP1</td>
<td>RAD52</td>
</tr>
<tr>
<td>0.25 - 0.5</td>
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<td>RAD21</td>
<td>RAD52</td>
<td>BRIP1</td>
</tr>
<tr>
<td>0</td>
<td>BRIP1</td>
<td>XRC4C</td>
<td>RAD21</td>
<td>RAD52</td>
</tr>
</tbody>
</table>

aOrder of entry of groups of predictors (following age) into the model.
bThese groups entered together.

by Gabriel et al. (2002), while the XRC4C SNPs fall in different haplotype blocks. Many of these SNPs are found to be associated with familial breast cancer in single SNP analyses. In marginal analysis, 14 SNPs have \(P < 0.05\). Ten of these are also selected by the mixed penalty method with \(\lambda_g/\lambda = 0.25 - 0.5\) (boldfaced in Table 1). It seems biologically reasonable that these SNP sets should be among the first predictors selected after age. SNP rs4986763 from gene BRIP1 is present in all models. This SNP is not found to be significant in previous single SNP analyses of the same goals at a fraction of the computational cost.

**REFERENCES**


