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Impact on Modes of Inheritance and Relative Risks of using Extreme Sampling When Designing Genetic Association Studies

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Summary

Using extreme phenotypes for association studies can improve statistical power. We study the impact of using samples with extremely high or low traits on the alternative model space, the genotype relative risks, and the genetic models in association studies. We prove the following results: when the risk allele causes high trait values, the more extreme the high traits, the larger the genotype relative risks, which is not always true for using extreme low traits; we also prove that a genetic model theoretically changes with more extreme trait except for the recessive or dominant models. Practically, however, the impact of deviations from the true genetic model at a functional locus due to selective sampling is virtually negligible. The implications of our findings are discussed. Numerical values are reported for illustrations.

Keywords

Association studies; Extreme sampling; Genetic models; Genotype relative risks; Replication

Introduction

Designs that use extreme high and low traits have been employed in both genetic linkage and association studies (Risch & Zhang, 1995; Forest & Feingold, 2000; Zheng et al., 2006). It has been shown that using extreme traits can improve statistical power for genetic association studies compared to the random sampling of all traits (Slatkin, 1999; Abecasis et al., 2001; Xiong et al., 2002; Chen et al., 2005; Chen & Li, 2011). The use of extreme high and low traits can be applied to design a case-control association study based on a threshold model. One such an example is described in Sims et al. (2008), who studied Wnt pathway genes for bone mass density (BMD) using 170 cases and 174 controls selected with high BMDs (Z -score from 1.51 to 3.97) and low BMDs (Z -score from -1.5 to -3.33), respectively, and demonstrated that using the extreme sampling can robustly detect genes of relevant effect sizes. A comparison between the use of extreme sampling and case-control data was reported by Yang et al. (2010). Extreme sampling has recently been applied to detect genes for rare variants (Guey et al., 2011; Li et al., 2011).

In this paper, we study the impact of extreme sampling on the alternative model space, the genotype relative risks (GRRs), and the modes of inheritance (genetic models). The GRRs

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are used in designing genetic association studies and genetic models play important roles in testing associations. The additive model, counting the number of the minor alleles in the genotype, is commonly used. Common non-additive models include the recessive and dominant models. When a genetic model is correctly specified, an optimal test is obtained and applied, which is sub-optimal when the model is mis-specified (Freidlin et al., 2002). If the genetic model changes substantially using extreme traits, which is likely because it is defined based on both phenotypes and genotypes, it may affect the power to detect association even though the samples with extreme traits are used. Moreover, it may also affect the interpretation of replication results when extreme traits are used in the replication.

Methods

Notation

Assume the marker of interest is in complete linkage disequilibrium (LD) with a disease locus. The alleles of the marker are denoted as b and B . Without loss of generality (WLG), when the marker is associated with a quantitative trait, let b be the risk allele, which causes a higher trait value. Three genotypes are denoted as G_i , where $i = 0, 1, 2$ counts allele b in the genotype. The frequency of G_i is denoted as $g_i = \text{pr}(G_i)$ ($i = 0, 1, 2$). Let X be a quantitative trait, given by $X/G = \mu + g + e$, where μ is the overall mean, g is the genetic value for the genotype G_i , and e is a non-genetic random error with mean $E(e) = 0$ and variance $\text{var}(e) = 1$ (WLG). Assume that G and e are independent. The value of g is given by $g = -a, d$ and a ($a > 0$) for $G = G_0, G_1$ and G_2 , respectively, where $d = -a, 0$, or a if the genetic model under the random sampling is recessive, additive, or dominant. We do not consider any under-dominant ($d < -a$) or over-dominant ($d > a$) models. WLG, let $\mu = 0$. Denote $E(X/G_i) = \mu_i$ and $(\mu_0, \mu_1, \mu_2) = (-a, d, a)$. Denote the conditional distribution of X given G_i as $X/G_i \sim F(x - \mu_i)$. The marginal distribution of X is $X \sim \sum_{i=0}^2 g_i F(x - \mu_i)$. The null hypothesis of no association is given by $H_0: a = d = 0$, under which $\mu_0 = \mu_1 = \mu_2 = 0$.

We consider a threshold model with the truncation points (u, v) , that is, we only sample individuals with $X > v$ or $X < u$, where $u < v$ are pre-specified in the design stage. If the distribution of X can be estimated using previous data (Xu et al., 1999), u and v can be chosen as its $100c_1$ th and $100(1 - c_2)$ th percentiles, respectively, where c_1 (c_2) can be, say, 0.01, 0.10, or 0.20. If an estimation is not available, one may consider using the extreme rank selection, which does not require an underlying distribution of X (Chen et al., 2005; Zheng et al., 2006). Define the study population as $X_S = \{X < u \text{ or } X > v, u < v\}$. Only individuals whose traits belong to X_S are genotyped. We call the design with X_S as extreme sampling. Sampling only high traits is a special case by letting $u \rightarrow -\infty$. Denote the penetrance for G_i as $p_i = \text{pr}(X > v/G_i, X_S) = (1 - F_{v,i})/(F_{u,i} + 1 - F_{v,i})$ ($i = 0, 1, 2$), where $F_{x,i} = F(x - \mu_i)$ for $x = u, v$. The GRRs are given by $\lambda_j = p_j/p_0$ ($j = 1, 2$). Under $H_0, a = d = 0$ is equivalent to $\lambda_1 = \lambda_2 = 1$ or $p_0 = p_1 = p_2$.

The model space under extreme sampling

Under the alternative hypothesis H_1 , one is more interested in the three common genetic models: recessive ($\mu_0 = \mu_1 < \mu_2$), additive ($\mu_0 < \mu_1 < \mu_2$ and $\mu_1 = (\mu_0 + \mu_2)/2$) and dominant ($\mu_0 < \mu_1 = \mu_2$) and any model between the recessive and dominant models. That is, without any under- and over-dominant models, the model space formed by (μ_0, μ_1, μ_2) under the random sampling of all traits can be written as $M = \{(\mu_0, \mu_1, \mu_2): \mu_0 \leq \mu_1 \leq \mu_2, \mu_0 < \mu_2\}$, which includes the three common genetic models. Define $\theta = (\mu_1 - \mu_0)/(\mu_2 - \mu_0)$ under H_1 . Hence, $\mu_1 = (1 - \theta)\mu_0 + \theta\mu_2$ and M can be indexed by θ as $M = \{\theta \in [0, 1]: \mu_1 = (1 - \theta)\mu_0 + \theta\mu_2\}$. The model space M under random sampling is constrained because θ only belongs to $[0, 1]$. Test statistics are more powerful under the constrained model space than

under the unconstrained model space: $H_1: \mu_0 \neq \mu_1 \neq \mu_2$ (Zheng et al., 2009a). Next, we first study if the model space in terms of GRRs (λ_1, λ_2) or penetrances (p_0, p_1, p_2) would be further constrained under extreme sampling.

Denote the density function of X given G_i as $f_{x,i} = f(x|\mu_i)$ ($i = 0, 1, 2$) and $r_{x,i} = f_{x,i}/(1-F_{x,i})$. Under extreme sampling, conditional on G , we assume (i) $r_{x,i}$ is an increasing function of x , (ii) $f_{x,i}$ is symmetric with respect to μ_i , i.e., $f(x|\mu_i) = f(-x|\mu_i)$, and (iii) $f_{x,i}$ is a decreasing function of $x > \mu_i$. These assumptions are all satisfied if the trait (after log or power transformation) follows a normal distribution. It can be shown that (iv) $f_{x,i}/F_{x,i}$ is a decreasing function of $x < \mu_i$ as follows. For $x < y < \mu_i$, $f_{x,i}/F_{x,i} = f(x|\mu_i)/F(x|\mu_i) = f(\mu_i - x)/\{1 - F(\mu_i - x)\} > f(\mu_i - y)/\{1 - F(\mu_i - y)\} = f_{y,i}/F_{y,i}$ due to $\mu_i - x > \mu_i - y$ and (i).

Let (μ_0, μ_1, μ_2) belongs to M . Then, under extreme sampling, we have $u < \mu_0 < u < \mu_1 < u < \mu_2$ and $v < \mu_0 < v < \mu_1 < v < \mu_2$. For $i > j$, $1 - F_{v,i} < 1 - F_{v,j}$ and $F_{u,i} > F_{u,j}$. It follows that $F_{u,i}/(1 - F_{v,i}) > F_{u,j}/(1 - F_{v,j})$, which is equivalent to $p_i > p_j$. Thus, if we define $M' = \{(p_0, p_1, p_2): p_0 > p_1 > p_2 \text{ and } p_0 < p_2\} = \{(\lambda_1, \lambda_2): \lambda_2 > \lambda_1 > 1 \text{ and } \lambda_2 > 1\}$, then for any $(\mu_0, \mu_1, \mu_2) \in M$, $(p_0, p_1, p_2) \in M'$ under extreme sampling, which leads to Result 1.

Result 1. *The constraints on the mean traits (μ_0, μ_1, μ_2) under the random sampling hold on the GRRs under extreme sampling. Thus, using extreme sampling does not further reduce the model space compared to the random sampling.*

Impact on the GRRs under extreme sampling

Why would using extreme traits improve power of association studies? Result 1 shows it is not due to a smaller model space. Hence, we study how GRRs change under extreme sampling. Write the GRRs as

$$\lambda_i(u, v) = \{(1 - F_{v,i})(F_{u,0} + 1 - F_{v,0})\} / \{(1 - F_{v,0})(F_{u,i} + 1 - F_{v,i})\}, \quad \text{for } i=1, 2.$$

Taking the partial derivatives of $\log \lambda_i$ with respect to u and v , we have, for any $u < v$,

$$\begin{aligned} \frac{\partial}{\partial u} \log \lambda_i &= \frac{f_{u,0}}{F_{u,0} + 1 - F_{v,0}} - \frac{f_{u,i}}{F_{u,i} + 1 - F_{v,i}} \\ \frac{\partial}{\partial v} \log \lambda_i &= \frac{f_{v,0}}{1 - F_{v,0}} - \frac{f_{v,i}}{1 - F_{v,i}} + \frac{f_{v,i}}{F_{u,i} + 1 - F_{v,i}} - \frac{f_{v,0}}{F_{u,0} + 1 - F_{v,0}} \\ &= (1 - p_0) r_{v,0} - (1 - p_i) r_{v,i}. \end{aligned}$$

We prove $\partial/\partial u \log \lambda_i < 0$ under some conditions and $\partial/\partial v \log \lambda_i > 0$ for any $u < v$. For any $u < \mu_0$, by property (iv), $f_{u,0}/F_{u,0} < f_{u,i}/F_{u,i}$. Then $\lim_{v \rightarrow \infty} \partial/\partial u \log \lambda_i = f_{u,0}/F_{u,0} - f_{u,i}/F_{u,i} < 0$. Thus, there exists $V > \mu_2$ such that for any $v > V$ and the given $u < \mu_0$, $\partial/\partial u \log \lambda_i < 0$. For the second one, since $1 - p_0 > 1 - p_i$ and $r_{v,0} > r_{v,i}$, we have $\partial/\partial v \log \lambda_i > 0$ for any $u < v$. In the above results, either u or v is fixed. When they both change, let $u = u(v)$ and denote $u'_v = \partial u / \partial v [GRH]_0$. Then,

$$\frac{\partial}{\partial v} \log \lambda_i = (1 - p_0) (r_{v,0} + r_{u,0} u'_v) - (1 - p_i) (r_{v,i} + r_{u,i} u'_v).$$

In order to have $\partial/\partial v \log \lambda_i > 0$, we only need

$u'_v [MGN] - \{(1 - p_0) r_{v,0} - (1 - p_i) r_{v,i}\} / \{(1 - p_0) r_{u,0} - (1 - p_i) r_{u,i}\}$. That is, u cannot decrease much faster than v increases. This leads to Result 2.

Result 2. When $f(x - \mu)/\{1 - F(x - \mu)\}$ is an increasing function of x and $f(x - \mu)$ is symmetric about μ , the GRRs monotonically increase either when v increases for a fixed $u < v$, or when u decreases for a fixed $v > u$ that is large enough, or when u decreases and v increases simultaneously provided that $v > u$ is large enough.

The result shows that when v is not extreme enough, going extreme on u alone (extreme low trait values) does not necessarily increase the GRRs. Practically, it implies that, if one chooses either $100(1 - c_2)$ th upper percentile for extremely high traits or $100c_1$ th lower percentile for extreme low traits for association studies, one should let c_2 be smaller than c_1 unless the cost of screening is a concern. On the other hand, using the thresholds $X < u$ and $X > v$, the probability that an individual will be selected for genotyping decreases as u becomes smaller and/or v becomes larger, and converges to 0 as $u \rightarrow -\infty$ and $v \rightarrow \infty$. Hence, there is a trade-off between the power/sample size and the cost of screening extreme samples.

We plot the values of GRR λ_2 due to extreme sampling with $d = 0$ and $u = K^{-1}(c_1)$ and $v = K^{-1}(1 - c_2)$, where $K(x) = q^2F(x + a) + 2pqF(x) + p^2F(x - a)$ and p the frequency of allele b and $q = 1 - p$. We choose $F(x) = \Phi(x)$ as the standard normal distribution. GRR $\lambda_2 = p_2/p_0$ given $a = 0.1$, $d = 0$ and $p = 0.3$ is presented in Figure 1, where $c_1(c_2) = 0.01$ (more extreme), 0.10, 0.20 (moderate extreme), 0.30 and 0.50. Figure 1 shows that the GRR increases with extreme high traits (larger v), but not necessarily for extreme low traits (smaller u), which depends on how extreme v is. The plots for other parameter values including various allele frequencies (e.g., $p = 0.15$ or 0.45 and other a and d) are similar (the results are not presented here).

The numerical values are also reported in Table 1 by focusing on the three scenarios: (a) $c_1 = c_2$ and both change, (b) c_1 is fixed but c_2 changes, and (c) c_2 is fixed but c_1 changes. Numerical values show that, when $p = 0.3$, $a = 0.1$ and $u = K^{-1}(0.2)$, λ_2 increases monotonically from 1.126 with $v = K^{-1}(0.50)$ to 1.496 with $v = K^{-1}(0.80)$, and up to 2.154 with $v = K^{-1}(0.99)$. Thus, choosing extreme low traits for a given v does not necessarily increase the GRRs.

Impact on genetic models under extreme sampling

The genetic model under the random sampling is indexed by θ such that $\mu_1 = (1 - \theta)\mu_0 + \theta\mu_2$ (i.e., $d = -(1 - \theta)a + \theta a$). Under the recessive, additive, and dominant models, $\theta = 0, 1/2, 1$, respectively. We study how the genetic models change from random sampling to extreme sampling. When $\theta = 0$ (or $\theta = 1$), i.e., $d = -a$ (or $d = a$), it is straightforward to show $p_0 = p_1$ (or $p_1 = p_2$). However, in general, when $\mu_1 = (1 - \theta)\mu_0 + \theta\mu_2$ for $\theta \in (0, 1)$, we do not have $p_1 = (1 - \theta)p_0 + \theta p_2$ with the same genetic model θ . The above arguments are summarized in Result 3.

Result 3. For any $u < v$, the recessive ($\theta = 0$) or dominant ($\theta = 1$) models under the random sampling will be retained under the extreme sampling. However, the genetic model indexed by $\theta \in (0, 1)$ under the random sampling will not be retained under the extreme sampling.

The above result shows that the additive model under the random sampling would not be the additive model under the extreme sampling, which depends on how (u, v) is chosen and the shape of the distribution of X . In particular, to retain the additive model under the extreme sampling from the random sampling, $u = K^{-1}(c_1)$ and $v = K^{-1}(1 - c_2)$ have to satisfy $1 - F(u) = F(v)$, under which $p_1 = \{1 - F(v - \mu_1)\}/\{F(u - \mu_1) + 1 - F(v - \mu_1)\} = \{1 - F(v)\}/\{F(u) + 1 - F(v)\} = 1/2$ (as $\mu_1 = 0$ under the additive model) and $p_0 = F(u - a)/\{F(u - a) + F(u + a)\}$ and $p_2 = F(u + a)/\{F(u - a) + F(u + a)\}$. Thus, $p_0 + p_2 = 1$, i.e., $p_1 = (p_0 + p_2)/2$, the additive model under the extreme sampling.

To examine the deviation of the genetic model under the extreme sampling from the genetic model under the random sampling, we define an induced model as $\theta^* = (c_1 - 1)/(c_2 - 1) = (p_1 - p_0)/(p_2 - p_0)$ and compare it to θ . The numerical values are reported in Table 2, which shows that θ^* is actually quite close to θ , especially when $c_1 = c_2 = c$, which corresponds to $u = K^{-1}(c)$ and $v = K^{-1}(1 - c)$. Allele frequency has little impact on the genetic models under the random sampling and extreme sampling. Hence, the power of testing association using extreme traits would be little or not affected when θ is used as the genetic model under extreme sampling even though θ^* is the true model.

Discussion

We have shown that, when using extreme high or low traits for association studies, the power is increased because the GRRs are increased and not because the model space (the space for the alternative hypothesis of association) is reduced. Although the genetic models are generally changed from random sampling to extreme sampling except for the recessive or dominant models, the changes are small so that the statistical power for association studies is not expected to be affected. Therefore, when the true genetic model is known, the same statistic used for analyzing the association under the random sampling should also be used for analyzing the association with extreme sampling. On the other hand, the true genetic model for many complex traits is rarely known. Genetic association studies based on a single genetic model may not be robust at all. Hence, robust tests (Freidlin et al., 2002; So & Sham, 2011) may be applied to detect association. Our results imply that the same robust tests under the random sampling can also be applied under extreme sampling. For replication studies, as far as the modes of inheritance and the model space are concerned, our results imply that it is valid to use samples with extreme traits, especially the higher traits, to replicate the results obtained based on random samples or less extreme traits. Finally, a limitation of our results is that they are derived when the marker is in complete LD with a functional locus. In practice, however, markers are likely in LD with the functional loci. In this case, the genetic models at the markers of interest are more complicated and may not be the same as those of the functional loci (Zheng et al., 2009b).

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Figure 1.

A plot of GRR λ_2 given $a = 0.1$, $d = 0$, $p = 0.3$, and $u = K^{-1}(c_1)$ and $v = K^{-1}(1-c_2)$ for $c_1(c_2) = 0.01$ (extreme truncation), 0.10, 0.20, 0.30, and 0.50.

Table 1

GRR λ_2 under extreme sampling given $a = 0.1$, $d = 0$, $p = 0.3$, and $u = K^{-1}(c_1)$ and $v = K^{-1}(1 - c_2)$. The smaller c_1 , the more extreme are the low trait values. The smaller c_2 , the more extreme are the high trait values. Results are reported for the three different scenarios (a)-(c).

GRR				
c_1	$c_2 = c_1$	$c_2 = 0.01$	$c_2 = 0.10$	$c_2 = 0.50$
0.01	1.614	1.614	1.072	1.012
0.10	1.387	2.201	1.387	1.082
0.20	1.303	2.154	1.496	1.126
0.30	1.248	2.087	1.527	1.150
0.50	1.167	1.966	1.517	1.167

GRR			
c_2	$c_1 = 0.01$	$c_1 = 0.10$	$c_1 = 0.50$
0.01	1.614	2.201	1.966
0.10	1.072	1.387	1.517
0.20	1.034	1.214	1.358
0.30	1.022	1.144	1.268
0.50	1.012	1.082	1.167

Table 2

The induced genetic model θ^* based on the GRRs under extreme sampling given $a = 0.1$, $d = (1 - \theta)(-a) + \theta a$, $p = 0.15$, 0.30 and 0.45 , and $u = K^{-1}(c_1)$ and $v = K^{-1}(1 - c_2)$. The entries are the values of θ^* given θ .

p	c_1	c_2	θ						
			0.1	0.3	0.5	0.7	0.9		
0.15	0.01	0.01	0.105	0.316	0.524	0.724	0.911		
		0.30	0.136	0.381	0.593	0.774	0.930		
		0.50	0.132	0.371	0.582	0.766	0.927		
	0.30	0.01	0.071	0.230	0.413	0.624	0.816		
		0.30	0.101	0.305	0.507	0.707	0.903		
0.30	0.01	0.50	0.109	0.321	0.525	0.721	0.909		
		0.50	0.01	0.074	0.236	0.421	0.631	0.869	
		0.30	0.093	0.284	0.481	0.685	0.894		
	0.30	0.50	0.100	0.301	0.502	0.702	0.901		
		0.01	0.102	0.308	0.514	0.715	0.908		
0.45	0.01	0.30	0.136	0.380	0.592	0.774	0.930		
		0.50	0.132	0.371	0.581	0.766	0.927		
		0.30	0.01	0.071	0.229	0.411	0.623	0.865	
	0.30	0.30	0.100	0.302	0.503	0.704	0.902		
		0.50	0.108	0.320	0.524	0.720	0.909		
0.45	0.01	0.50	0.01	0.073	0.235	0.420	0.630	0.869	
		0.30	0.093	0.283	0.480	0.684	0.893		
		0.50	0.100	0.301	0.501	0.701	0.901		
	0.30	0.01	0.098	0.299	0.503	0.707	0.905		
		0.30	0.136	0.379	0.591	0.773	0.930		
0.45	0.01	0.50	0.132	0.371	0.581	0.765	0.927		
		0.30	0.01	0.070	0.228	0.410	0.621	0.865	
		0.30	0.099	0.300	0.501	0.702	0.901		
	0.30	0.50	0.108	0.318	0.522	0.719	0.908		
		0.01	0.073	0.235	0.420	0.630	0.869		
0.45	0.01	0.30	0.092	0.282	0.479	0.682	0.893		

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θ						
p	c_1	c_2	0.1	0.3	0.5	0.9
			0.100	0.300	0.500	0.701
			0.50			0.900