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Identifying modifier loci in existing genome scan data

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Abstract

In many genetic disorders in which a primary disease-causing locus has been identified, evidence for additional trait variation due to genetic factors exists. These findings have led to studies seeking secondary "modifier" loci. Identification of modifier loci provides insight into disease mechanisms and may provide additional screening and treatment targets. We believe that modifier loci can be identified by re-analysis of genome screen data while controlling for primary locus effects. To test this hypothesis, we simulated multiple replicates of typical genome screening data on to two real family structures from a study of hypertrophic cardiomyopathy. With this marker data, we simulated two trait models with characteristics similar to one measure of hypertrophic cardiomyopathy. Both trait models included 3 genes. In the first, the trait was influenced by a primary gene, a secondary "modifier" gene, and a third very small effect gene. In the second, we modeled an interaction between the first two genes. We examined power and false positive rates to map the secondary locus while controlling for the effect of the primary locus with two types of analyses. First, we examine Monte Carlo Markov chain (MCMC) simultaneous segregation and linkage analysis as implemented in Loki, for which we calculated two scoring statistics. Second, we calculate LOD scores using an individual-specific liability class based on the quantitative trait value. We find that both methods produce scores that are significant on a genome-wide level in some replicates. We conclude that mapping of modifier loci in existing samples is possible with these methods.

Keywords

Modifier gene; Complex trait; Statistical Genetics; Monte Carlo Markov chain; linkage analysis

Introduction

In diseases in which a major gene has been identified, some evidence for "modifier" genes exists (Dipple & Mccabe, 2000a). Such evidence is often in the form of excess familial resemblance in disease phenotype, beyond what can be explained by the genotype at the major gene. In addition, when one looks beyond the simple summary of disease provided by

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binary affection status, the quantitative phenotypes associated with disease are generally more complex in their etiology (Dipple & Mccabe, 2000b). For example, cystic fibrosis was once seen as a monogenic disorder, with mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene causing the disease (Riordan *et al*., 1989). More recently, however, it was recognized that CFTR did not explain all the variation seen in cystic fibrosis and that quantitative measures captured a greater complexity than simple affectation status (Davies *et al*., 2005). These findings led to several studies in which secondary “modifier” loci were sought. A number of polymorphisms in other genes have now been identified that appear to modify disease severity in cystic fibrosis. As another example, mutations in p53 were identified as causing Li-Fraumeni syndrome (Malkin *et al*., 1990), but now additional loci have been found (Bachinski *et al*., 2005). The identification of such loci is important to provide insight into disease mechanisms and may provide screening and treatment targets.

Previously, it has been suggested that candidate gene approaches, mouse models, and sibling pair methods can be used to identify modifier genes (Houlston & Tomlinson, 1998). To date, several modifier genes have been identified via candidate gene studies, for example, in hearing loss (Schultz *et al*., 2005, Nadeau, 2005) and cystic fibrosis (Drumm *et al*., 2005, Haston & Hudson, 2005). When the genetic pathways involved are well understood, such searches can be fruitful. However, not all genetic pathways have been well documented, and even in pathways that have been documented, it is possible that all genes in the pathway have not yet been determined. This possibility has led us to consider another complementary approach to identify modifier loci.

We believe that it is possible to identify some modifier loci via linkage analysis of genome screen data while controlling for the effects of the primary locus. To test this hypothesis, we have examined the ability of LOD score methods (Shete *et al*., 2002) and Monte Carlo Markov chain oligogenic simultaneous segregation and linkage analysis (Heath, 1997) to identify a modifier gene in simulated data.

Simulated Data

The data we simulated was designed to be similar to a real data set available to us: two families confirmed to have a disease-causing mutation in the MyBP-C gene. Information was available on 2 real family 5-generation structures with 206 people. In both families, there is a single founder pair, their children, grandchildren, great grandchildren, and great-great grandchildren, along with the spouses of the descendents. The larger pedigree contained 125 people with the two founders, their 10 children and their 8 spouses, the 32 grandchildren and their 9 spouses, the 53 great grandchildren and their 4 spouses, and 7 great-great grandchildren. The second pedigree contained 81 individuals, with 2 founders, their 8 children and 6 spouses, 27 grandchildren and 11 of their spouses, 26 great grandchildren, one of whom had a spouse, and 1 great-great grandchild. While these pedigrees are large, they have no loops and are similar to large pedigrees seen in many other studies. On to these pedigrees, we simulated traits and genetic markers, with different values for each simulation. We chose to use a quantitative measure for the analysis because use of quantitative traits for genetic analysis is more powerful approach than dichotomizing the

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data to affected/unaffected (Wijsman & Amos, 1997). The simulated trait models were based on the results of oligogenic segregation analysis of real data using the software package Loki (Heath, 1997). These results indicated three genes, including the primary, "causative," gene. Thus, the first simulated trait model was affected by three genes: a primary gene, G_1, with a 10% disease allele frequency and dominant effect; a secondary "modifier" gene, G_2, with a 30% deleterious allele frequency and semi-additive effect; a third small effect gene, G_3, with a 40% deleterious allele frequency and an additive effect. The simulated trait value was given by:

$$Trait = \mu + G_1 + G_2 + G_3 + e$$

where: $\mu = 1.0$, the genetic effects were $G_1 \in \{0,0.7,0.7\}$, $G_2 \in \{0,0.2,0.7\}$, $G_3 \in \{0,0.05,0.1\}$, according to whether the individual was of genotype AA, AB, or BB at each locus, and e is a normally distributed residual with mean 0 and variance 0.12. The effects of G_1 and G_2 together are summarized in table I.

The second trait model we simulated had the same allele frequencies and same marginal effect for G_2, but included an interaction between G_1 and G_2 such that G_2 only had an effect if there was a disease allele at G_1 (See Table II). While an infinite array of interaction models might be possible, we chose this model to match the marginal effects for the modifier gene that we estimated in the real data. The two models can be compared in tables I and II. This model allows us to get some indication of the issues that interactions will cause.

The simulated genetic marker data was also designed to be similar to real marker data. We used the positions and allele frequencies for Marshfield mapping panel 8a markers. These markers are microsatellites and are at intervals of ~10cM. We simulated 98 markers on six chromosomes 9 through 14. The primary gene, G_1, was unlinked to these six simulated chromosomes, while the modifier gene, G_2, was placed on chromosome 11. Both marker loci and trait genes were simulated via the Genedrop program from the PANGAEA package (http://www.stat.washington.edu/thompson/Genepi/pangaea.shtml). A total of 100 replicates with 6 chromosomes each (one linked, five unlinked) were simulated for analysis. All 600 chromosomes were analyzed with both analytical methods for both traits.

Analytical Methods

We considered two methods for analysis: scores for Monte Carlo Markov chain (MCMC) oligogenic simultaneous segregation and linkage analysis and LOD scores. With both methods, we sought to identify the modifier locus, G_2, while accounting for the effect of the primary locus, G_1. Details of the MCMC oligogenic simultaneous segregation and linkage analysis can be found in Heath, 1997, while details of the LOD score approach we apply here can be found in (Shete *et al*., 2002). The software used included the Loki package (versions 2.4.7 and 2.4.8) for the MCMC methods and FASTLINK for the LOD score methods. We describe each of these methods in brief.

In the MCMC analysis, MCMC process samples the model space iteratively, with frequency of samples estimating posterior probability. The genotypes of locus G_1 were used as a

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covariate and the effect size was estimated. The other estimated parameters include the number of additional genes contributing to the trait, the effects of those genes, and the linkage position of those additional genes, if they are linked to markers in the analysis. To interpret the posterior probabilities generated by these methods, we used the "L-scores" produced by the Loki package via the included "dist.pl" script. These "L-scores" are computed in 1cM intervals. They are the posterior probability of linkage over the prior probability of linkage in each interval. An L-score of 1 indicates no information. Regions with linkage are expected to produce L-scores > 1. Exactly what threshold should be used for declaring significance is the subject of ongoing research. Here, we used the empirical null distribution provided by the MCMC analysis of the 500 chromosomes not linked to G_2 to establish significance levels for each trait simulation.

In addition to L-scores, we also computed LOP (Daw *et al*., 2003) for the MCMC analysis runs. The LOP compares evidence for linkage on the real chromosome with information on a simulated pseudo chromosome. It is the log of the ratio of the posterior probability of linkage on the real chromosome over that on the pseudo chromosome. As a score for oligogenic segregation and linkage analysis, it is computed over a 2-dimensinal grid of location on the chromosome and QTL variance contribution.

The LOD scores were calculated using an individual-specific liability class based on the quantitative trait value and mutation status at G_1. With this method, each individual is assigned a unique liability class and a normal probability density function is used for the liability class. The mean and variance of the normal density function were obtained based on trait value and mutation status of the first gene, G_1. The MLINK module of the software program FASTLINK was then used to obtain LOD scores. To maintain comparability with the results of the MCMC analyses, we also used the empirical null distribution provided by LOD score analysis of the 500 unlinked chromosomes to set significance cut-offs for each trait.

Results

Linkage was detected in some replicates with both MCMC and LOD score methods. In tables III, IV, and V, we present the distributions of maximum chromosome-wide LOP, L-scores, and LOD scores for all 100 replicates of the first trait model. Tables VI, VII, and VIII provide the corresponding values for the second trait. Values at each quartile, the 95th percentile, the 5th percentile, and the minimum and maximum are shown for each simulated chromosome, for all null (unlinked) chromosomes combined, and for all chromosomes (both null and linked) combined. The 95th percentile of the distribution of maximum chromosome-wide LOPs on unlinked (null) chromosomes is 2.23 for the first trait model. We find that 53% of the replicates give us a LOP on the linked chromosome that is greater than 2.23. Thus, we have a 53% empirical power with the LOP at a 5% level of significance. For the L-scores, the 95th percentile was 7.3, which gave us an even better 60% empirical power with MCMC methods at 5% level of significance. For the LOD scores, the 95th percentile was 1.33 and this gave us 33% empirical power with LOD score methods at 5% level of significance. In table IX, we present the empirical power for other significance cut-offs for both trait model simulations. In general, power is not as good for under the second

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simulated trait model, where G_1 and G_2 interacted. The only exception was for the LOD score method at the 5% significance level (see table IX). However, at higher significance levels, the LOD score method performed more poorly. For the most stringent cut-off, the maximum of the empirical null distribution, the power was best with the LOP for both trait models (last row of table IX). In the first simulated trait model, the empirical power was better with the MCMC methods at all significance levels. In the second simulated trait model, with the explicit interaction effect, the power at the 5% level was higher for the LOD score method, but at more stringent significance levels, the MCMC methods did better. Both methods show promise for identifying modifier loci in existing data sets, and while the MCMC methods appear to have better power in most of the situations examined here, there are some cases where the LOD score methods do better.

The computation time of both methods makes them feasible for linkage analysis of even very large samples. The MCMC methods required ~4 hours per chromosome on a 2GHz PowerPC G5 processor, and these methods scale linearly with sample size. The LOD methods required only a trivial amount of CPU time, less than 1 minute per chromosome.

Discussion

Our results indicate that linkage mapping of modifier loci in existing samples is possible. The power was generally greater with the MCMC methods than with the LOD score methods for the first simulated trait model, but there are some situations in which the LOD score methods have greater power. With either method, the human time required for a careful analysis will likely exceed the computer time for both methods together, and much of the set up for the two methods (e.g. Mendelian inheritance checks) is common to both methods. Thus, given the minimal computational burden of the LOD score methods, we recommend using both methods as one or the other may have advantages in different data sets.

While 30% to 60% power is less than what is generally desirable in a new study, in the context of a follow-up analysis of genetic marker and phenotype data that has been gathered to map a primary disease-causing gene, such analysis seems worthwhile. The costs are small compared to starting a new study. Furthermore, if time has passed since the initial data collection, re-contacting the families and collecting updated data and additional family members (if available) would increase power. We have recently applied these methods to map modifier loci in the real data upon which we based this simulation (Daw *et al*., 2007). While the markers we simulated were modeled on microsatellites, these methods can also be applied to SNPs (Daw *et al*., 2005). The methods examined here are a relatively low-cost first step in the search for modifier loci.

A linkage study for modifier loci has the advantage that it can identify modifier genes without previous knowledge of the gene’s function. While knowledge of a gene’s function is very useful in selecting candidate loci, there are still many genes with undocumented function. Conversely, as the functions of an ever greater number of genes are determined, it seems that plausible candidate genes for most phenotypes exist in most regions of the

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genome. Methods such as these can be used to narrow as well as identify a set of candidate modifier genes.

We have examined two scenarios out of the infinite set of models that could be viewed as modifier loci and found that searching for modifier loci in both of them could prove fruitful. Both these simulations were constructed to mimic the evidence we found for modifier loci we found in real data. The first scenario is a “modifier” locus in that it is a smaller effect locus that acts in addition to the main effect locus. The second scenario is a modifier in that it acts only in the presence of the disease causing mutation. We are interested in finding genes under both scenarios and think that there is a large overlap in the methodology useful for identifying “modifier” genes in these two cases, and one may not be able to identify which of these simulation models is closer to the true model until after the gene is identified. Another issue is that these methods search for modifier genes of a quantitative trait relating to the disease phenotype. If there are multiple quantitative measures, these analyses can be conducted on each of them. The genes found for each such quantitative trait may or may not be the same, but are likely to have an effect on disease risk. While it is possible that such a locus might not have a direct effect on disease susceptibility, its identification could lead to better understanding of the disease biology and could, for example, increase the prognostic value of the quantitative measure by controlling for the gene’s effects.

With a sample size of ~200 individuals in large families, we can detect modifier loci. There are a large number of family studies that have collected a sufficient sample size and data to which these methods can be applied. These approaches can also be applied to smaller family units. However, as with any linkage analysis, unit of information is the number of informative meioses and so smaller family units (e.g. sib pairs) will require a larger number of individuals be sampled. A more subtle modifier effect than the ones we simulated may require a slightly larger sample size, but many family studies have data on well more than 200 people. In our own study (Daw et al., 2007), we were able to apply these methods to identify four modifier loci. Since many of these studies have already collected the requisite data in identifying primary genetic causes of disease, the main costs of conducting such a study are the time of a statistical geneticist and the cost of the computational resources.

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Table I

Effects and marginals of first model (no interaction between G_1 and G_2)

	G_1:	**AA**	**Aa**	**aa**	
G_2:	~Marginal effect	0	0.7	0.7	
BB	0	0	0.7	0.7	0.49
Bb	0.2	0.2	0.9	0.9	0.42
bb	0.7	0.7	1.4	1.4	0.09
		0.81	0.18	0.01	Marginal frequency

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Table II

Effects and Marginals of second model (With G_1 by G_2 interaction)

	G_1:	**AA**	**Aa**	**aa**	
G_2:	~Marginal effect	0	1.3252	1.3252	
BB	0	0	0.7	0.7	0.49
Bb	0.2	0	1.75	1.75	0.42
bb	0.7	0	4.38	4.38	0.09
		0.81	0.18	0.01	Marginal frequency

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Table III

Maximum chromosome-wide LOP distributions, first model

	min	5%	25%	50%	75%	95%	max
chr11 (true)	0.74	0.87	1.52	2.34	3.22	3.71	3.90
chr10 (null)	0.70	0.81	0.95	1.15	1.48	2.28	2.89
chr12 (null)	0.70	0.80	0.97	1.20	1.71	2.29	3.01
chr13 (null)	0.70	0.81	0.95	1.04	1.41	2.20	2.72
chr14 (null)	0.70	0.85	0.95	1.04	1.32	2.26	2.74
chr9 (null)	0.70	0.81	0.95	1.11	1.42	1.99	3.00
All null Chr	0.70	0.85	0.95	1.11	1.45	2.23	3.01
All Chr	0.70	0.85	0.95	1.20	1.72	3.09	3.90

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Table IV

Maximum chromosome-wide L-score distributions, first model

	min	5%	25%	50%	75%	95%	max
chr11 (true)	0.24	0.48	1.69	10.44	47.17	120.43	177.43
chr10 (null)	0.14	0.24	0.38	0.85	1.90	8.15	30.81
chr12 (null)	0.10	0.21	0.46	0.85	2.11	9.04	26.27
chr13 (null)	0.14	0.22	0.39	0.65	1.39	5.83	37.72
chr14 (null)	0.15	0.25	0.40	0.70	1.21	6.32	14.43
chr9 (null)	0.15	0.21	0.41	0.79	1.32	6.83	23.89
All null Chr	0.10	0.22	0.41	0.76	1.50	7.30	37.72
All Chr	0.10	0.23	0.44	0.87	2.33	38.21	177.43

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Table V

Maximum chromosome-wide LOD distributions, first Model

	min	5%	25%	50%	75%	95%	max
chr11 (true)	0.10	0.22	0.71	1.11	1.61	2.93	3.62
chr10 (null)	-0.07	0.09	0.22	0.43	0.73	1.36	1.86
chr12 (null)	0.01	0.09	0.28	0.46	0.72	1.32	2.14
chr13 (null)	-0.03	-0.01	0.13	0.40	0.74	1.46	2.65
chr14 (null)	-0.03	0.03	0.24	0.44	0.68	1.32	2.21
chr9 (null)	0.03	0.14	0.28	0.53	0.77	1.29	1.85
All null Chr	-0.07	0.03	0.22	0.44	0.73	1.33	2.65
All Chr	-0.07	0.04	0.25	0.50	0.85	1.76	3.62

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Table VI

Maximum chromosome-wide LOP distributions, second model

	min	5%	25%	50%	75%	95%	max
chr11 (true)	0.85	0.90	1.58	2.08	3.01	3.71	3.85
chr10 (null)	0.78	0.87	1.08	1.51	1.92	2.61	3.13
chr12 (null)	0.78	0.85	1.04	1.37	1.78	2.39	2.79
chr13 (null)	0.60	0.78	0.95	1.18	1.82	2.72	3.57
chr14 (null)	0.60	0.85	0.95	1.26	1.64	2.36	3.08
chr9 (null)	0.70	0.78	1.04	1.41	1.96	2.99	3.71
All null Chr	0.60	0.85	1.00	1.34	1.85	2.60	3.71
All Chr	0.60	0.85	1.04	1.41	1.94	3.13	3.85

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Table VII

Maximum chromosome-wide L-score distributions, second model

	min	5%	25%	50%	75%	95%	max
chr11 (true)	0.20	0.44	1.88	5.10	39.36	191.31	303.87
chr10 (null)	0.13	0.31	0.75	1.69	3.78	22.63	52.71
chr12 (null)	0.15	0.25	0.63	1.33	3.35	12.08	44.10
chr13 (null)	0.13	0.22	0.52	0.99	2.52	20.94	127.34
chr14 (null)	0.15	0.29	0.80	1.57	3.25	10.85	64.05
chr9 (null)	0.16	0.28	0.87	1.78	5.37	45.25	220.80
All null Chr	0.13	0.27	0.67	1.46	3.53	25.64	220.80
All Chr	0.13	0.28	0.75	1.76	4.54	49.99	303.87

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Table VIII

Maximum chromosome-wide LOD distributions, second Model

	min	5%	25%	50%	75%	95%	max
chr11 (true)	0.02	0.13	0.40	0.83	1.36	2.47	4.59
chr10 (null)	0.00	0.05	0.34	0.53	0.99	1.57	2.65
chr12 (null)	-0.01	0.06	0.25	0.55	0.87	1.51	2.04
chr13 (null)	-0.10	0.04	0.16	0.40	0.71	1.26	1.87
chr14 (null)	0.00	0.04	0.24	0.46	0.77	1.53	1.81
chr9 (null)	0.00	0.10	0.27	0.56	0.91	1.37	1.60
All null Chr	-0.10	0.05	0.24	0.49	0.84	1.44	2.65
All Chr	-0.10	0.06	0.27	0.50	0.93	1.68	4.59

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Table IX

Empirical power for finding the modifier locus with different scores for both trait models

Empirical significance cut off	Score					
	LOP		L-score		LOD	
	Trait 1	Trait 2	Trait 1	Trait 2	Trait 1	Trait 2
>95%	53%	37%	60%	31%	33%	48%
>99%	42%	22%	43%	19%	19%	17%
>max null	32%	4%	30%	2%	8%	3%