

snpBMA: a package for details genetic association analysis of densely typed genetic regions

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1 Bayesian Model Averaging and the BMA package

2 Priors

3 Simulate some data

We start with using some sample data from the `snpStats` package including 20 SNPs, and simulating a quantitative trait that depends on 3 causal SNPs.

```
> library(snpStats)
> data(for.exercise, package="snpStats")
> X <- snps.10[,11:30]
> n <- nrow(X)
> set.seed(12346)
> Y <- rnorm(n,mean=as.numeric(X[,1]))*sqrt(0.1) +
+   rnorm(n,mean=as.numeric(X[,5]))*sqrt(0.1) +
+   rnorm(n,mean=as.numeric(X[,11]))*sqrt(0.1) +
+   rnorm(n)*sqrt(0.7)
> (causal <- colnames(X)[c(1,5,11)])
```

```
[1] "rs4880781" "rs6560730" "rs2448365"
```

X contains some missing genotypes, but no SNPs with such a low call rate we would worry in a large study. Still, the rest of the analysis is easier to interpret for the purposes of a vignette if we fill in the missing values.

```
> summary(X)
```

```
$rows
```

Call.rate	Certain.calls	Heterozygosity
Min. :0.8500	Min. :1	Min. :0.0000
1st Qu.:1.0000	1st Qu.:1	1st Qu.:0.0500
Median :1.0000	Median :1	Median :0.2500
Mean :0.9908	Mean :1	Mean :0.2379
3rd Qu.:1.0000	3rd Qu.:1	3rd Qu.:0.3000
Max. :1.0000	Max. :1	Max. :0.8500

```
$cols
```

Calls	Call.rate	Certain.calls	RAF
Min. :985.0	Min. :0.9850	Min. :1	Min. :0.05635
1st Qu.:989.8	1st Qu.:0.9898	1st Qu.:1	1st Qu.:0.18880
Median :991.0	Median :0.9910	Median :1	Median :0.49625
Mean :990.8	Mean :0.9908	Mean :1	Mean :0.50807
3rd Qu.:992.0	3rd Qu.:0.9920	3rd Qu.:1	3rd Qu.:0.93542
Max. :996.0	Max. :0.9960	Max. :1	Max. :0.94708

MAF	P.AA	P.AB	P.BB
Min. :0.05292	Min. :0.004032	Min. :0.09778	Min. :0.00404
1st Qu.:0.06447	1st Qu.:0.006564	1st Qu.:0.11885	1st Qu.:0.04385
Median :0.07493	Median :0.266493	Median :0.13780	Median :0.25900
Mean :0.16779	Mean :0.372936	Mean :0.23800	Mean :0.38907
3rd Qu.:0.25653	3rd Qu.:0.668380	3rd Qu.:0.35928	3rd Qu.:0.87588
Max. :0.42828	Max. :0.891371	Max. :0.47879	Max. :0.89819

```
z.HWE
```

```
Min. :-3.3051
1st Qu.: -1.4680
Median : -0.7586
Mean : -1.0221
3rd Qu.: -0.4576
Max. : 0.3150
```

```
> X <- impute.missing(X)
```

```
20 to impute
```

```
1 .SNPs tagged by multiple tag haplotypes (saturated model): 1
2 .SNPs tagged by a single SNP: 1
3 .SNPs tagged by a single SNP: 1
```

```

4 .SNPs tagged by multiple tag haplotypes (saturated model): 1
5 .SNPs tagged by a single SNP: 1
6 .SNPs tagged by multiple tag haplotypes (saturated model): 1
7 .SNPs tagged by a single SNP: 1
8 .SNPs tagged by a single SNP: 1
9 .SNPs tagged by multiple tag haplotypes (saturated model): 1
10 .SNPs tagged by multiple tag haplotypes (saturated model): 1
11 .SNPs tagged by a single SNP: 1
12 .SNPs tagged by a single SNP: 1
13 .SNPs tagged by multiple tag haplotypes (saturated model): 1
14 .SNPs tagged by multiple tag haplotypes (saturated model): 1
15 .SNPs tagged by multiple tag haplotypes (saturated model): 1
16 .SNPs tagged by multiple tag haplotypes (saturated model): 1
17 .SNPs tagged by a single SNP: 1
18 .SNPs tagged by multiple tag haplotypes (saturated model): 1
19 .SNPs tagged by a single SNP: 1
20 .SNPs tagged by multiple tag haplotypes (saturated model): 1

```

```

coercing object of mode numeric to SnpMatrix

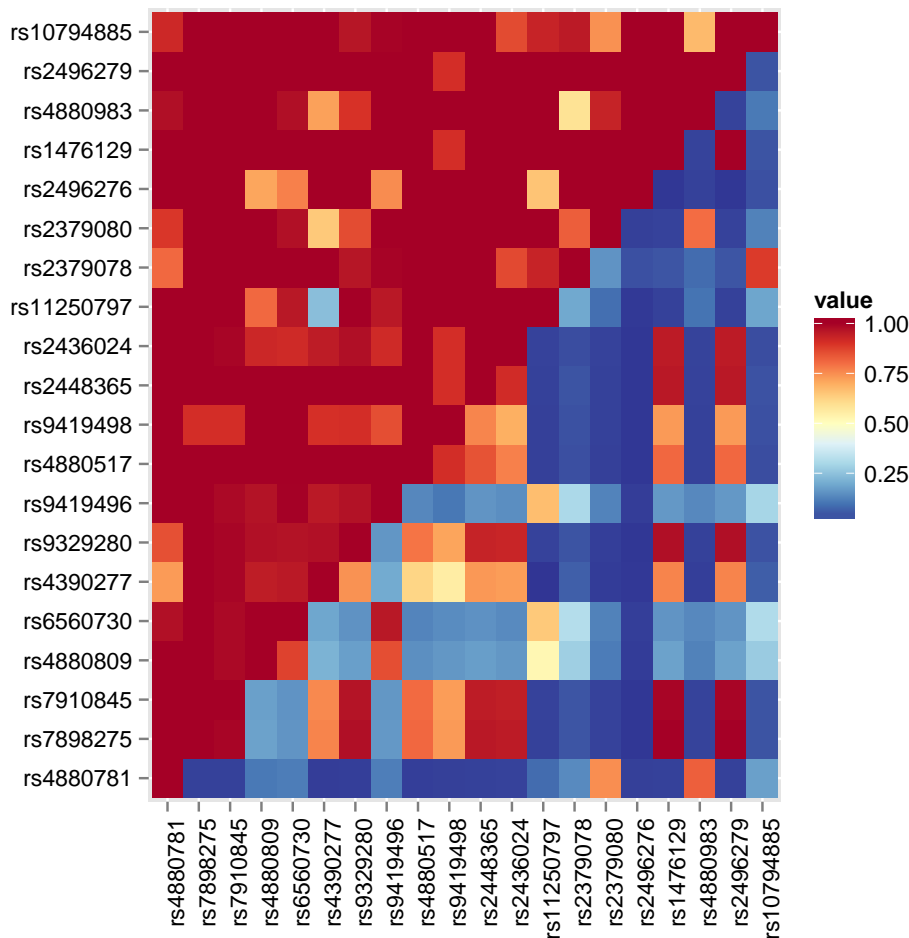
```

Looking at the LD, we see this is a region in which D' (above the diagonal) is very high, whilst r^2 can be high between some SNPs, and with moderately strong $r^2 \simeq 0.7$ between two of our causal SNPs:

```

> ld <- show.ld(X=X)

```



4 Using BMA to identify the causal variants

Bayesian model averaging approaches can be slow when the number of SNPs is very large, as the number of models grows rapidly. The simulated data are deliberately small here, so that you can compare the effect of the different ways we tackle this, which fall into three categories:

5 A full BMA analysis using SNP tagging to quickly cover the model space

First, we aim to cover the model space more rapidly by focusing on a tagging subset of SNPs, then expand to include the tagged SNPs only in the neighbourhood of supported models. Tags can be selected using the `tag` function, where `tag.threshold` sets the r^2 threshold used to group SNPs. This function makes use of `hclust` to do the grouping. We can see that not all of our causal SNPs will be analysed directly, but some through tags.

```
> tags <- tag(X, tag.threshold=0.8)
> tags[causal]
```

```
rs4880781 rs6560730 rs2448365
"rs4880781" "rs4880809" "rs7898275"
```

Now we can consider sets of models, fixing the number of SNPs each time.

```
> ## make a snpBMAdat set
> data <- make.data(X, Y, tags=tags, family="gaussian")
```

Keeping 1000 of 1000 samples and 9 SNPs

```
> ## Calculate Bayes Factors for all one SNP models
> bma.1 <- bma.nsnps(data, nsnps=1)
```

groups not needed, creating a model matrix of 9 x 9 .
Evaluating 9 models

```
> ## Summarise the SNPs with greatest support
> head(ss1 <- snp.summary(bma.1))
```

```
6 x 3 Matrix of class "dgeMatrix"
      twologB10-phi1 twologB10-phi2 twologB10-phi3
rs2379078      43.771987      42.799868      40.597782
rs4880781      16.319267      15.331546      13.121382
rs7898275      11.429279      10.438779       8.227175
rs4880809      10.332114       9.340991       7.129064
rs4880517       7.108734       6.115778       3.902903
rs4390277       5.986209       4.992616       2.779411
```

Although the `bma.nsnps()` function works for any number of SNPs, it can be simpler to think of growing your BMA models from a parent generation (here, all possible one SNP models) to a child generation (here, all possible two SNP models).

```
> bma.2 <- bma.grow(data=data, bma=bma.1)
```

Evaluating 36 models

```
> bma.3 <- bma.grow(data=data, bma=bma.2)
```

Evaluating 84 models

```
> bma.4 <- bma.grow(data=data, bma=bma.3)
```

Evaluating 126 models

5.1 Visualizing the results

It can be nice to visualize the support across these generations of models graphically. So far, we have assumed each model within a generation has an equal prior, which seems reasonable in the absence of specific information about the likely impact of each SNP. However, it doesn't seem reasonable that all models, regardless of the number of SNPs, should have equal priors. Models with smaller numbers of SNPs should be favoured. We can implement this by specifying a prior for the number of SNPs in a model. `snpBMA` has two functions to do this, or you can just create your own numeric vector.

```
> ## assume a binomial prior for the number of SNPs with expectation of 3 causal SNPs
> ## ie exactly the scenario simulated!
> priors <- prior.binomial(1:10, n=ncol(X), expected=3)
```

See the help for `prior.betabinomial` to understand the other function available, and the difference to a binomial prior.

```
> ## create a graph of BMA results so far
> results <- stack(bma.1,bma.2,bma.3,bma.4)
> g<-graphBMA(bma.list=results, priors)
> ## g is an igraph, so you can do all the usual stuff with it:
> g
```

```
[[1]]
```

```
[1] 255
```

```
[[2]]
```

```
[1] FALSE
```

```
[[3]]
```

```
  [1]   9   9  10  10  11  11  12  12  13  13  14  14  15  15  16  16  17  17
 [19]  18  18  19  19  20  20  21  21  22  22  23  23  24  24  25  25  26  26
 [37]  27  27  28  28  29  29  30  30  31  31  32  32  33  33  34  34  35  35
 [55]  36  36  37  37  38  38  39  39  40  40  41  41  42  42  43  43  44  44
 [73]  45  45  45  46  46  46  47  47  47  48  48  48  49  49  49  50  50  50
 [91]  51  51  51  52  52  52  53  53  53  54  54  54  55  55  55  56  56  56
[109]  57  57  57  58  58  58  59  59  59  60  60  60  61  61  61  62  62  62
[127]  63  63  63  64  64  64  65  65  65  66  66  66  67  67  67  68  68  68
[145]  69  69  69  70  70  70  71  71  71  72  72  72  73  73  73  74  74  74
[163]  75  75  75  76  76  76  77  77  77  78  78  78  79  79  79  80  80  80
[181]  81  81  81  82  82  82  83  83  83  84  84  84  85  85  85  86  86  86
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[217]  93  93  93  94  94  94  95  95  95  96  96  96  97  97  97  98  98  98
[235]  99  99  99 100 100 100 101 101 101 102 102 102 103 103 103 104 104 104
[253] 105 105 105 106 106 106 107 107 107 108 108 108 109 109 109 110 110 110
[271] 111 111 111 112 112 112 113 113 113 114 114 114 115 115 115 116 116 116
[289] 117 117 117 118 118 118 119 119 119 120 120 120 121 121 121 122 122 122
```

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[343]	133	133	134	134	134	134	135	135	135	135	136	136	136	136	137	137	137	137
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[379]	142	142	143	143	143	143	144	144	144	144	145	145	145	145	146	146	146	146
[397]	147	147	147	147	148	148	148	148	149	149	149	149	150	150	150	150	151	151
[415]	151	151	152	152	152	152	153	153	153	153	154	154	154	154	155	155	155	155
[433]	156	156	156	156	157	157	157	157	158	158	158	158	159	159	159	159	160	160
[451]	160	160	161	161	161	161	162	162	162	162	163	163	163	163	164	164	164	164
[469]	165	165	165	165	166	166	166	166	167	167	167	167	168	168	168	168	169	169
[487]	169	169	170	170	170	170	171	171	171	171	172	172	172	172	173	173	173	173
[505]	174	174	174	174	175	175	175	175	176	176	176	176	177	177	177	177	178	178
[523]	178	178	179	179	179	179	180	180	180	180	181	181	181	181	182	182	182	182
[541]	183	183	183	183	184	184	184	184	185	185	185	185	186	186	186	186	187	187
[559]	187	187	188	188	188	188	189	189	189	189	190	190	190	190	191	191	191	191
[577]	192	192	192	192	193	193	193	193	194	194	194	194	195	195	195	195	196	196
[595]	196	196	197	197	197	197	198	198	198	198	199	199	199	199	200	200	200	200
[613]	201	201	201	201	202	202	202	202	203	203	203	203	204	204	204	204	205	205
[631]	205	205	206	206	206	206	207	207	207	207	208	208	208	208	209	209	209	209
[649]	210	210	210	210	211	211	211	211	212	212	212	212	213	213	213	213	214	214
[667]	214	214	215	215	215	215	216	216	216	216	217	217	217	217	218	218	218	218
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[793]	246	246	246	246	247	247	247	247	248	248	248	248	249	249	249	249	250	250
[811]	250	250	251	251	251	251	252	252	252	252	253	253	253	253	254	254	254	254

[[4]]

[1]	0	1	0	2	0	3	0	4	0	5	0	6	0	7	0	8	1	2
[19]	1	3	1	4	1	5	1	6	1	7	1	8	2	3	2	4	2	5
[37]	2	6	2	7	2	8	3	4	3	5	3	6	3	7	3	8	4	5
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[[5]]

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[595]	594	595	596	597	598	599	600	601	602	603	604	605	606	607	608	609	610	611
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[667]	666	667	668	669	670	671	672	673	674	675	676	677	678	679	680	681	682	683
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 [145] "#FF0000FF" "#FF0000FF" "#FF0000FF" "#FF0000FF" "#FF0000FF" "#FF0000FF"
 [151] "#FF0000FF" "#FF0000FF" "#FF0000FF" "#FF0000FF" "#FF0000FF" "#FF0000FF"
 [157] "#FF0000FF" "#FF0000FF" "#FF0000FF" "#FF0000FF" "#FF0000FF" "#FF0000FF"
 [163] "#FF0000FF" "#FF0000FF" "#FF0000FF" "#FF0000FF" "#FF0000FF" "#FF0000FF"
 [169] "#FF0000FF" "#FF0000FF" "#FF0000FF" "#FF0000FF" "#FF0000FF" "#FF0000FF"
 [175] "#FF0000FF" "#FF0000FF" "#FF0000FF" "#FF0000FF" "#FF0000FF" "#FF0000FF"
 [181] "#FF0000FF" "#FF0000FF" "#FF0000FF" "#FF0000FF" "#FF0000FF" "#FF0000FF"


```

[111] 2.446315e+07 8.929893e+01 2.951713e-02 4.972038e+06 2.591590e+04
[116] 1.110147e-01 9.127474e+06 5.642092e+07 1.389128e+01 1.725300e+07
[121] 6.244869e+05 6.442445e-01 4.037865e+07 2.024304e+08 2.920743e+01
[126] 2.002605e+06 8.294033e+07 2.491470e+00 2.511625e+07 7.212397e+08
[131] 3.020800e+08 6.056267e+09 7.099224e+08 3.713083e+08 1.525051e+08
[136] 9.415050e+03 1.687908e+10 2.245939e+08 1.538441e+04 4.049843e+03
[141] 5.983385e+09 1.330362e+08 1.721506e+04 4.511905e+03 5.824849e+09
[146] 6.979071e+09 3.519622e+09 6.945730e+08 1.978772e+08 7.520424e+03
[151] 7.633304e+07 2.583904e+07 5.746876e+07 3.331037e+07 1.262817e+07
[156] 2.605759e+08 2.437922e+08 1.306024e+08 5.206620e+07 3.073207e+07
[161] 1.274114e+07 4.862062e+06 8.316435e+07 2.203228e+07 8.498028e+06
[166] 8.962648e+07 2.320674e+07 2.322727e+03 5.364538e+02 1.647128e+07
[171] 4.476725e+06 1.550661e+06 4.606236e+07 1.263304e+07 3.666631e+02
[176] 2.608670e+08 1.363543e+08 5.728841e+07 2.011014e+08 5.639204e+07
[181] 6.611146e+02 4.941609e+06 2.919895e+06 1.359407e+02 7.428932e+07
[186] 3.641176e-01 1.257023e+00 4.394778e+06 2.292341e+05 1.651367e-01
[191] 8.019771e-01 1.918922e+06 8.983347e+04 1.126790e-01 2.451115e+06
[196] 1.067784e+06 3.476777e-01 4.071195e+06 1.699546e+07 4.277614e+04
[201] 1.274513e+00 7.852684e+06 2.686350e+01 6.714660e-03 3.979989e+06
[206] 3.333332e+06 5.563913e-01 9.929272e+06 5.527857e+07 1.140201e+01
[211] 1.539025e+06 1.093457e+06 3.508049e-01 4.650654e+06 1.654650e+07
[216] 1.245390e+01 8.670014e+06 1.065877e+07 5.939628e+05 1.217980e+07
[221] 5.159134e-02 4.485035e+05 1.854186e+04 2.187563e-02 1.599953e+05
[226] 5.714339e+03 8.898152e-03 3.048068e+05 1.431943e+06 3.088449e+03
[231] 5.126500e+05 4.536617e+04 3.015232e-02 1.276389e+06 5.625039e+06
[236] 1.234544e+04 2.618054e+05 2.662528e+06 1.283893e+03 7.558653e+05
[241] 4.065944e+05 1.663804e+04 1.799060e-02 9.320683e+05 5.175369e+06
[246] 1.236408e+00 1.940937e+05 2.021865e+06 4.045455e+02 1.100759e+06
[251] 1.222542e+06 5.160454e+06 1.049243e+04 4.275469e+06 3.072533e+06

```

```

[[9]][[4]]
list()

```

```

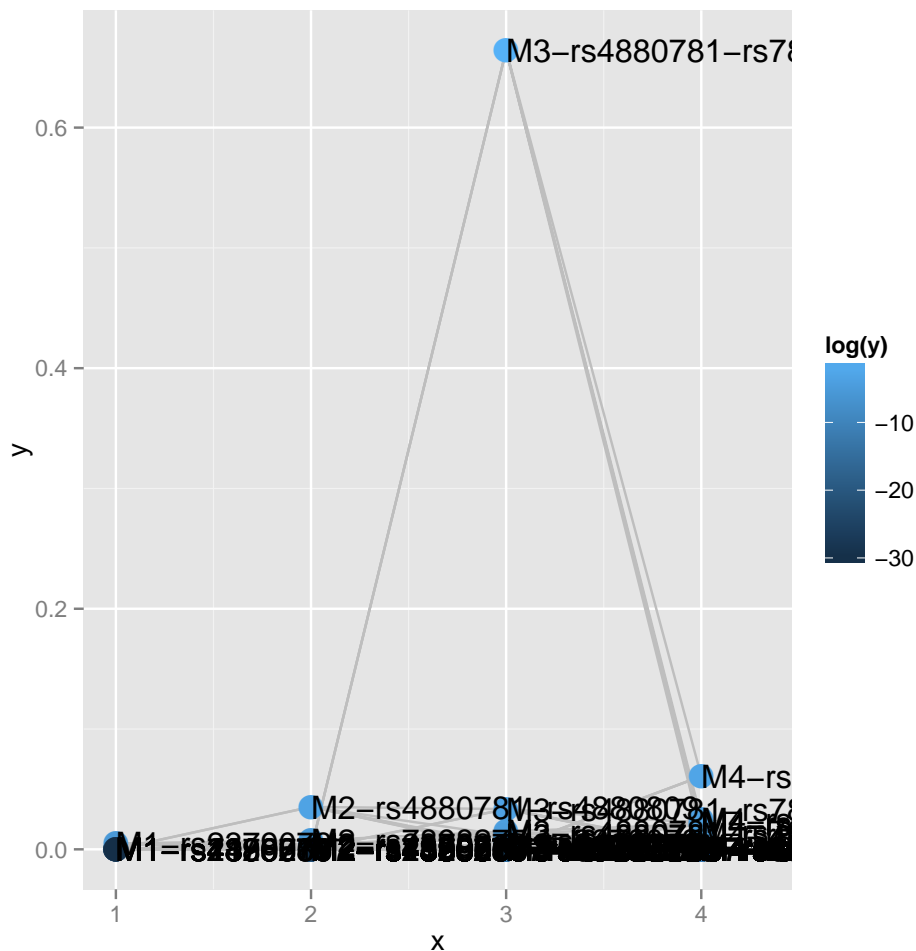
attr(,"class")
[1] "igraph"

```

```

> ## visualize
> graphView(g)

```



This shows the models according to posterior probabilities **across the model space visited**. One model stands out, with SNPs 0, 1 and 5. These are 0-based numeric indices of the SNPs included, and we can identify these SNPs using:

```
> snps0(bma.3)[ as.character(c(0,1,5)) ]
```

```
      0      1      5
"rs4880781" "rs7898275" "rs11250797"
```

but it can be easier just write the top models to screen

```
> top.models(results, priors)
```

	PP_phi=phi.1	PP_phi=phi.2	PP_phi=phi.3
rs4880781-rs7898275-rs11250797	0.60675646	0.66432568	0.649646424
rs4880781-rs7898275-rs4390277-rs11250797	0.08977791	0.06076187	0.019811840
rs4880781-rs4880809	0.01971501	0.03528005	0.104034328
rs4880781-rs7898275-rs4880809	0.03090777	0.03347557	0.032552474
rs4880781-rs7898275-rs11250797-rs2379080	0.03753353	0.02512349	0.008144521
rs4880781-rs7898275-rs4880809-rs11250797	0.03277594	0.02180155	0.007044701

5.2 Add back in the tagged SNPs

We used tagging to span the space quickly. Once we have found our favoured models, it makes sense to see how the tagged SNPs in LD with SNPs in those models change things. There are a couple of subtleties here to be aware of however:

1. the X matrix must be of full rank, which means a small amount of tagging may always be necessary, say at $r^2=0.99$
2. when two SNPs are in strong LD, fitting both in the model can make the model uninterpretable. With snpBMA you can group SNPs so that at most one of each group is included in any single model. The default grouping threshold is $r^2=0.8$, but the optimal value will depend on your data: with many subjects a higher threshold may be appropriate, as the SNPs become statistically distinguishable.

```
> ## First, tag at r2=0.99
> tags.99 <- tag(X, 0.99)
> ## group remaining snps at r2=0.8, using the first set of tags above as indices
> groups <- group.tags(tags, keep=tags.99)
> length(groups)
```

```
[1] 9
```

```
> data.99 <- make.data(X, Y, tags=tags.99, family="gaussian")
```

Keeping 1000 of 1000 samples and 17 SNPs

Now we decide which tag SNP groups we would like to "expand". We choose any SNPs in the top three models, after which the posterior probabilities appear to tail off:

```
> top.models(results, priors)
```

	PP_phi=phi.1	PP_phi=phi.2	PP_phi=phi.3
rs4880781-rs7898275-rs11250797	0.60675646	0.66432568	0.649646424
rs4880781-rs7898275-rs4390277-rs11250797	0.08977791	0.06076187	0.019811840
rs4880781-rs4880809	0.01971501	0.03528005	0.104034328
rs4880781-rs7898275-rs4880809	0.03090777	0.03347557	0.032552474
rs4880781-rs7898275-rs11250797-rs2379080	0.03753353	0.02512349	0.008144521
rs4880781-rs7898275-rs4880809-rs11250797	0.03277594	0.02180155	0.007044701

```
> expand.snps <- top.snps(results, priors, nmodels=3)
```

Now we can refit all models including these tagged SNPs in their groups:

```
> bma.e1 <- bma.expand(data.99, bma.1, groups=groups[expand.snps])
```

Evaluating 15 models

```
> bma.e2 <- bma.expand(data.99, bma.2, groups=groups[expand.snps])
```


Evaluating 95 models

```
> bma.e3 <- bma.expand(data.99, bma.3, groups=groups[expand.snps])
```

Evaluating 335 models

```
> bma.e4 <- bma.expand(data.99, bma.4, groups=groups[expand.snps])
```

Evaluating 729 models

You can see the model space grows much more quickly. But the end result is not dissimilar:

```
> ## create a graph of BMA results so far
> expand.results <- stack(bma.e1,bma.e2,bma.e3,bma.e4)
> g.expand<-graphBMA(expand.results, priors)
> ## visualize
> graphView(g.expand)
> top.models(expand.results, priors)
```

	PP_phi=phi.1	PP_phi=phi.2	PP_phi=phi.3
rs4880781-rs2436024-rs11250797	0.20913526	0.23578576	0.25168354
rs4880781-rs2448365-rs11250797	0.07981117	0.08980140	0.09575663
rs4880781-rs9329280-rs11250797	0.05623972	0.06326127	0.06744644
rs4880781-rs7898275-rs11250797	0.05353557	0.06023917	0.06423529
rs4880781-rs2436024-rs9419496	0.05286495	0.05904594	0.06272170
rs4880781-rs2448365-rs9419496	0.03208448	0.03581346	0.03803065

