

Gene-Gene Interaction Analysis for Bipolar Disorder

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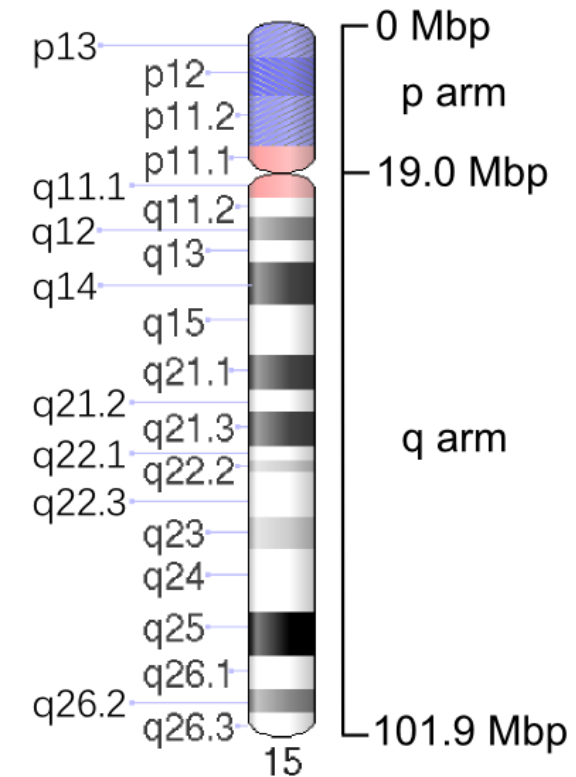
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Bipolar Disorder

- Bipolar disorder, also known as manic-depressive illness, is a brain disorder that causes unusual shifts in mood, energy, activity levels, and the ability to carry out day-to-day tasks.
- Prevalence of bipolar disorder: 4%
- Heritability of bipolar disorder: 82%
- Although many clues show that bipolar disorder is caused by some genetic factors, missing heritability makes hard to explain genetic mechanism of bipolar disorder.

Genetic relationship between schizophrenia and bipolar disorder



- Chromosome locus 15q26 has been identified as a candidate region for both schizophrenia and bipolar disorder in a whole-genome linkage study of eastern Quebec families with combined schizophrenia and bipolar disorder.
- ST8SIA2 (ST8 alpha-N-acetyl-neuraminide alpha-2, 8-sialyltransferase 2 gene) is one of the candidate genes for psychiatric illnesses mapping to this region.
- Our previous study found that ST8SIA2 is related with bipolar disorder and schizophrenia in Korean population.

ST8SIA2 study



RESEARCH ARTICLE

Association between *ST8SIA2* and the Risk of Schizophrenia and Bipolar I Disorder across Diagnostic Boundaries

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- A total of 582 patients with schizophrenia, 339 patients with bipolar disease, and 502 healthy controls were included.
- The associations were evaluated by logistic regression analysis using additive, dominant, and recessive genetic models.

ST8SIA2 study

Schizophrenia + BD-I (N = 762)

SNP	P ^a	OR	CI	Best-fit model ^b
rs3759915	0.102	1.236	0.959– 1.594	Dominant
rs4777969	0.014*	0.806	0.678– 0.957	Additive
rs8025225	0.131	0.782	0.569– 1.076	Recessive
rs4777973	0.004*	1.405	1.113– 1.774	Dominant
rs11637898	0.0006**	1.492	1.186– 1.878	Dominant
rs4777980	0.002*	1.440	1.143– 1.814	Dominant
rs3784737	0.249	1.144	0.910– 1.437	Dominant

- Thirty-four SNPs were analyzed.
- The inheritance model with the least Akaike Information Criterion was accepted as the best fitting model.
- We controlled the experiment-wise type I error using the Bonferroni correction.
- rs11637898 has the significant p-value after Bonferroni correction.

Finding the additional genetic marker for the same population

- After ST8SIA2 study, we performed additional target gene (Gene A) study with the same population.
- Twenty-eight SNPs were analyzed.
- We controlled the experiment-wise type I error using the FDR q-value.
- Some SNPs in the target gene A have the q-value below 0.05.

	beta	sd(beta)	t-statistic	nominal p-value	q-value
Additive	0.350396	0.12076	2.90159	0.003713	0.041933
Dominant	0.377263	0.135652	2.781114	0.005417	0.059818
Recessive	0.644307	0.422914	1.523493	0.127635	0.404884

Gene x Gene interaction analysis between ST8SIA2 and GENE A

- If we find the gene-gene interaction effect between ST8SIA2 and gene A for bipolar disorder 1 and schizophrenia samples, we could contribute to reveal missing heritability.
- We checked the gene-gene interaction effects between the two SNPs which were selected by the lowest p-value in each gene.
- To analyze gene-gene interaction we considered two schemes.
 - Logistic regression based analysis.
 - Multifactor Dimensionality Reduction (MDR) based method.

Previous Gene X Gene interaction analysis with logistic regression.

RESEARCH ARTICLE

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PART
B

Interaction Between Genetic Variants of *DLGAP3* and *SLC1A1* Affecting the Risk of Atypical Antipsychotics-Induced Obsessive–Compulsive Symptoms

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- In previous study, we found the gene x gene interaction between *DLGAP3* and *SLC1A1* for obsessive-compulsive symptoms based on logistic regression.

Gene x Gene interaction analysis with Logistic regression scheme.

- $logit(\pi_i) = \beta_0 + \gamma_1 Age + \gamma_2 Sex + \beta_1 SNP_1 + \beta_2 SNP_2 + \beta_3 SNP_1 * SNP_2$
- SNP_1 and SNP_2 were used by the combination of additive, recessive, dominant models. Thus, there are nine models for two SNPs.
- To find the optimal model between nine models, we selected the model which has the smallest AIC values.

Results of Gene x Gene interaction analysis with Logistic regression

- $logit(\pi_i) = \beta_0 + \gamma_1 Age + \gamma_2 Sex + \beta_1 SNP_1 + \beta_2 SNP_2 + \beta_3 SNP_1 * SNP_2$
- P-values are calculated for $H_0: \beta_3 = 0$

AIC		ST8SIA2		
		add	dominant	recessive
GENE A	add	1559.434	1563.286	1563.735
	dominant	1562.083	1566.043	1564.966
	recessive	1567.36	1567.845	1570.894

p-value		ST8SIA2		
		add	dominant	recessive
GENE A	add	0.000711	0.005083	0.008464
	dominant	0.001389	0.010766	0.007572
	recessive	0.035918	0.042192	0.437145

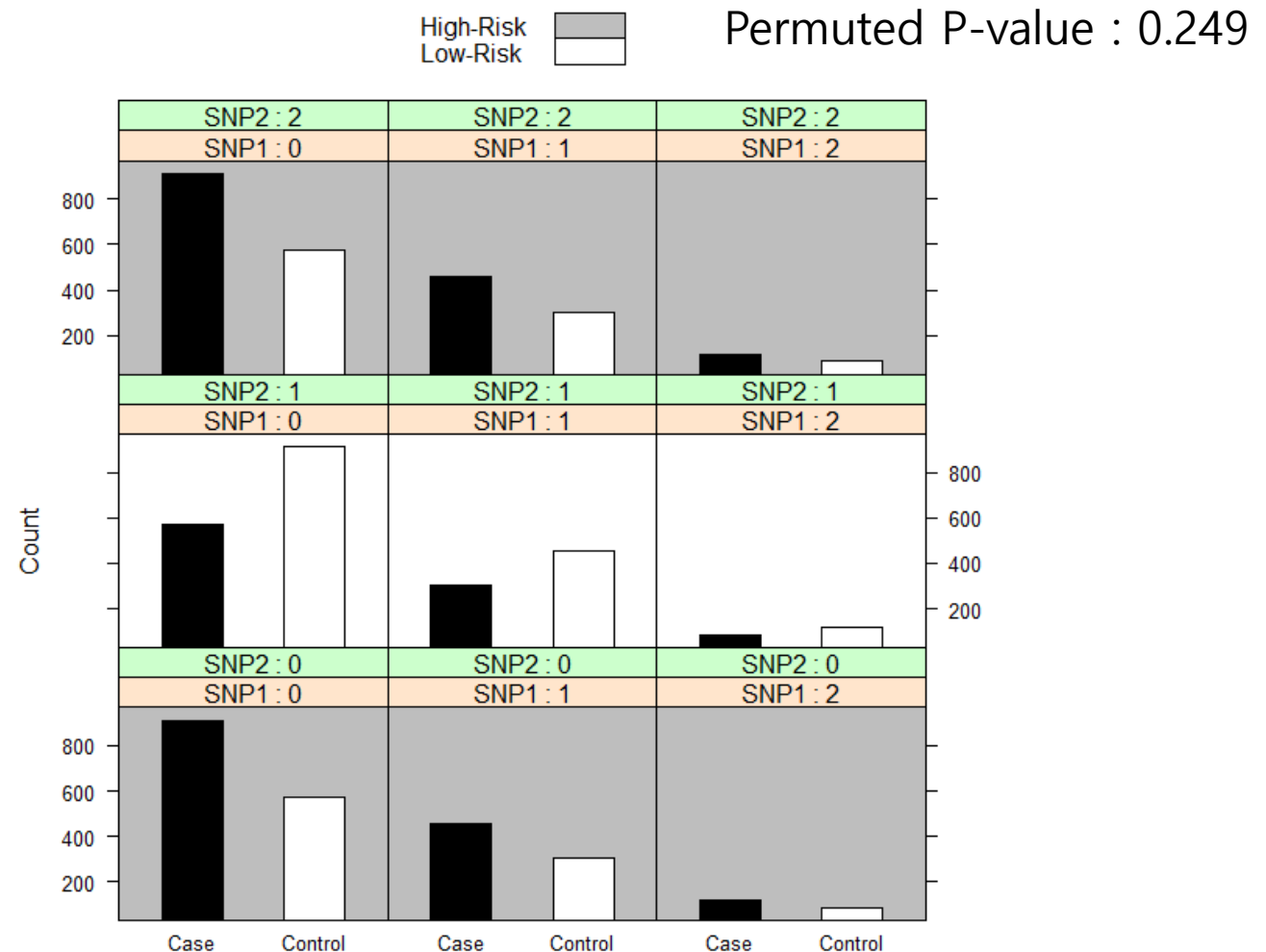
Gene x Gene interaction analysis with Logistic regression between ST8SIA2 and GENE A

	Estimate	Std.Error	Z-value	Pr(> z)
(Intercept)	-0.10601	0.299892	-0.354	0.72371
age	0.030519	0.006954	4.389	1.14E-05 ***
sex	-0.29509	0.121772	-2.423	0.01538*
ST8SIA2	0.075639	0.094753	0.798	0.42471
GENE A	0.313048	0.259492	1.206	0.22767
ST8SIA2:GENE A	-0.81481	0.248624	-3.277	0.00105 **

- Interaction term of ST8SIA2 and GENE A was significant when both genes were coded by additive.
- Age is highly significant factor for bipolar I disorder and schizophrenia.

Gene x Gene interaction analysis with MDR

- Perform 10-fold cross validation (CV) with the selected combination.
- Model classification performance is evaluated by balanced accuracy.
- Training set classification accuracy : 52.83 (%)
- Test set classification accuracy : 51.95 (%)



Results of Gene x Gene interaction analysis with Logistic regression

- $logit(\pi_i) = \beta_0 + \beta_1 SNP_1 + \beta_2 SNP_2 + \beta_3 SNP_1 * SNP_2$
- P-values are calculated for $H_0: \beta_3 = 0$

With age, sex adjust

Without age, sex adjust

AIC		ST8SIA2		
		add	dominant	recessive
GENE A	add	1559.434	1563.286	1563.735
	dominant	1562.083	1566.043	1564.966
	recessive	1567.36	1567.845	1570.894

AIC		ST8SIA2		
		add	dominant	recessive
GENE A	add	1580.133	1584.499	1583.783
	dominant	1582.48	1586.928	1584.839
	recessive	1588.615	1589.087	1591.297

p-value		ST8SIA2		
		add	dominant	recessive
GENE A	add	0.000711	0.005083	0.008464
	dominant	0.001389	0.010766	0.007572
	recessive	0.035918	0.042192	0.437145

p-value		ST8SIA2		
		add	dominant	recessive
GENE A	add	0.000689	0.006622	0.005741
	dominant	0.001215	0.012482	0.004976
	recessive	0.060642	0.071835	0.450518

Conclusion

- We found that gene A shows significant relationship with bipolar disorder I and schizophrenia samples.
- After finding the significant gene, we tried gene-gene interaction analysis with gene A and ST8SIA2 by two schemes: logistic regression and MDR.
- By logistic regression we could find significant interaction term between gene A and ST8SIA2.
- With or without covariate adjust, interaction terms in logistic regression are significant.
- In MDR analysis, however, the SNP pair did not significant with permutation p-value.

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