Bayesian Prognostic Model for Genomic Discovery in Bipolar Disorder

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Abstract: Integrative approaches that incorporate multiple experiments have shown a potential application in the discovery of disease-related attributes. This study presents a unique, data-driven, integrative, Bayesian approach to merge gene expression data from various experiments into prognostic models and evaluate them for the discovery of bipolar-related attributes. Two prognostic models were constructed: a singly-structuredBayesian and a Bayesian multi-net model, which differentiated Bipolar disease state at a higher level of abstraction. These prognostic models were evaluated to find the most common attributes responsible for the disease and their AUROC, using external crossvalidation.

The multi-net model achieved an AUROC of 0.907 significantly outperforming the single-structured model with an AUROC of 0.631. The study found six new genes and five chromosomal regions associated with the bipolar state. Enrichment analysis performed in this study revealed biological concepts and proteins responsible for the disease. We anticipate this method and results will be used in the future to integrate information from multiple experiments for the same or related phenotypes of variousdiseases and also to predict the disease state earlier.

1 INTRODUCTION

Over the past ten years, the emergence of high-throughput genetic data has presented a new opportunity for the development of diagnostic and prognostic tools for disease and the discovery of new disease-related genes (Clark et al., 2001), (Collins et al., 2003). Previous studies have shown an improvement in discovering disease-related attributes by integrating the phenotypic content of many experiments (Aerts et al., 2006), (Calvo et al., 2006), (Freudenberg et al., 2002), (English et al., 2007). Traditionally, however, these approaches have been verified through comparison to gold standard gene lists, which are themselves the products of previous experiments. This is an arbitrary method of validation, and even more ominously, shifts the focus of bioinformatics research away from discovery.

In the present study, we use a completely data-driven Bayesian approach to discover bipolar disorder attributes and validate them without resorting to *a priori* information knowledge bases.

The topic of bipolar disorder warrants further study for proper prevention and cure, as Bipolar disorder (Beynon et al., 2009), (Schiffer, 2007), (Benazzi, 2007), (Morriss et al., 2007), (Sachs et al., 2007) affects approximately 5.7 million adult Americans, or about 2.6% of the U.S. population age 18 and older every year and results in 9.2 years reduction in expected life span, and as many as one in five patients with bipolar disorder completes suicide as per the National Institute of Mental Health. Bipolar disorder causes a condition in which people go back and forth between periods of a very good or irritable mood and depression. The "mood swings" between mania and depression can be very quick.

Current diagnostic techniques like medication, talk therapy depict Success rates of 70 to 85% with lithium for the acute phase treatment of mania. However, lithium response rates of only 40 to 50% are now commonplace. The diagnosis is also

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sometimes misdiagnosed with depression in women and schizophrenia in men. But the studyof high throughput gene expression data shows potential in developing more accurate prognostic and diagnostic methods for fast prevention and cure of the disease.

The main goal of the present study is to create unifying predictive models across multiple experiments and to enable accurate prognosis and diagnosis of Bipolar disorder. The statistical modelling in this study is based on Bayesian networks. Bayesian networks are directed acyclic graph structures that extend Bayesian analysis (Pearl, 1988), and are a set of multivariate probabilistic models that have increased the power in learning and classification due to their compact factorization of data (Alterovitz, 2007), (Sebastiani et al., 2005). Bayesian networks are powerful in their ability to learn conditional relationships from large datasets and to use this probability distribution to classify other instances based on their feature values. When they are used to represent biological systems (Table S - 1), Bayesian networks create models of simultaneous genetic associations and dependencies, as well as genetic interplay with clinical and environmental variables (Sebastiani et al., 2005). These models are capable of capturing weak epistatic dependencies between genes, and previous studies have used Bayesian networks to analyze many types of genome-scale data, including genotype data (Sebastiani et al., 2005), gene expression date (Friedman, 2004), and protein-protein interactions.

Furthermore, the presented approach identifies genes, biological functions, and pathways related to disease that can serve as the basis for future studies.

Many construction approaches exist for Bayesian networks. The NaiveBayes classifier, which requires only a small amount of training data to estimate the parameters (Mean and Variance of the variables) necessary for classification is used in this model to perform external cross-validation. Depending on the precise nature of the probability model, naive Bayes classifiers are trained very efficiently in a supervised learning setting. This prognostic model can be used to improve the accuracy of classification for a single phenotype across multiple classes of patients as well as different but related phenotypes.

In this project, Naïve Bayes classifier (Harry, 2004), (Caruana and Niculescu-Mizil, 2006), (George and Pat Langley) is used to integrate several bipolar disorder phenotypes in a predictive setting.

Table S-1: Classification of samples collected from Bipolar disorder patients – Actual class Vs Predicted class (Control, GDS2190 and GDS2191).

		Predicted Class		
		Control	GDS2190	GDS2191
Actual Class	Control	38	4	0
	GDS2190	10	20	0
	GDS2191	1	0	9

2 MATERIALS AND METHODS

2.1 Data Mining and Collection

Two Gene Expression Omnibus (GEO) datasets from NCBI were used in this study and are stored in GDS2190 and GDS2191 in various forms of the Affymetrix microarray platform (Dalma-Weiszhausz et al., 2006). These two GDS datasets correspond to previous genome-scale experiments that relate to bipolar disorder related phenotypes:

(1) GDS2190 (Ryan et al., 2006) contains 61 samples of GPL96, taken from homo-sapiens;

(2) GDS2191 (Ryan et al., 2006) contains 21 samples of platform GPL96, taken from Homo-Sapiens

Total number of samples that correspond to Control, GDS2190 and GDS2191 are shown in Table(S-1) and plotted in Figure 1. For each GDS, genes corresponding to multiple Affymetrix Probe IDs were collapsed down to the maximum value. The gene expression datawere normalized through the reasonable assumption that the total gene product in each individual is approximately equal. The normalization was done by setting all means and variances equal to the reference mean and variance of data in GDS2190, such thatμ = μGDS2190 and σ = σGDS2191. This second normalization step was done in order to merge the controls from all experiments.

2.2 Finding Differentially Expressed Genes

Differentially expressed genes were found using the Bioconductor package (Gentleman et al., 2005). Moderated t-statistics (R Documentation, http://rss.acs.unt.edu/) with Benjamini-Hochberg multiple hypothesis correction(Benjamini and Hochberg, 1995) ranked the top differentially expressed genes of bipolar disorder infected patients versus controls for each experiment by p-value. Analyses were done to construct two prognostic models of significant genes. The gene obtained from Variance filtering of each experimental gene list was compiled, and the genes in common across these lists were considered the shared-feature set.

2.2.1 Algorithm in R (to Generate Prognostic Models)

1. Determine the Gene ID’s for Bipolar disorder
2. Find ALL Common Genes across all Gene ID’s
3. Separate the samples according to Control Vs non-Control
4. Find Common Top differentially expressed genes for each experiment
5. Create "interesting reduced experiments" (IREs), which are essentially data tables that represent each of the interesting experiments and their expression data from each GSM sample. They are "reduced" because only the data from the common genes is included in each data table.
6. Normalize IREs by using a reference IRE, finding its median, and subtracting the difference between the reference median and the IRE's median from each value in the IRE
7. Binarize the expValues for 1’s and 0’s
8. Create ARFF files stored as .txt file with the data from these genes

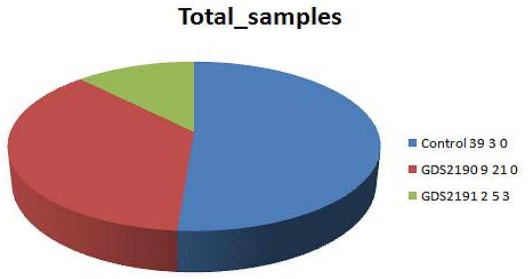


Figure 1: Classification of samples collected from the Bipolar disorder patients through GDS2190 and GDS2191 datasets, taken from NCBI.

2.3 Construction of Classifier and Evaluation using External Crossvalidation

For the present study, Weka GUI was used to find the ‘best set of features’, build a classifier and implement External Cross validation on the top differentially expressed binarized genes to calculate their AUROC. Linear forward selection search method was used to filter the best attributes from a given larger set. The evaluator evaluated the attributes using an independent feature model called Naïve Bayes classifier which assumes that the presence (or absence) of a particular feature of a class is unrelated to the presence (or absence) of any other feature. While the search method is Extension of BestFirst. It takes a restricted number of k attributes into account. Fixed-set selects a fixed number k of attributes, whereas k is increased in each step when fixed-width is selected. The search uses either the initial ordering to select the top k attributes, or performs a ranking (with the same evaluator the search uses later on). The search direction can be forward or floating forward selection (with optional backward search steps).

In external crossvalidation, thesamples were divided into 10 subsets of approximately equal size. In each iteration, nine subsets were used to find a common-feature set and train the model. The final subset is used to test the model. This procedure is essential to correct the bias induced through feature selection step. The Area Under Receiver Operating Characteristic (AUROC) curve in Figure 2 was estimated by averaging the AUROCs across the ten folds.

2.3.1 Algorithm in Weka (to Perform External Crossvalidaton)

1. Convert the .txt file obtained from R pipeline into weka supported .arff file.
2. Extract the Best set of features using AttributeSelectionClassifier in Weka GUI
3. Use Training Set to evaluate the Results of External Cross-validation and calculate the AUROC

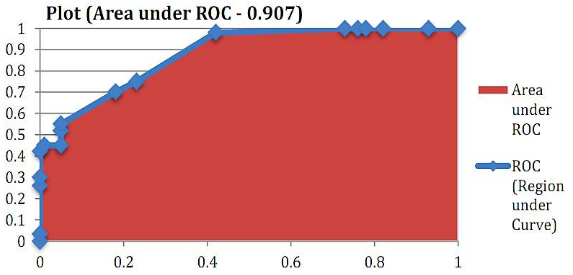


Figure 2: Threshold curve with an AUROC of 0.907.

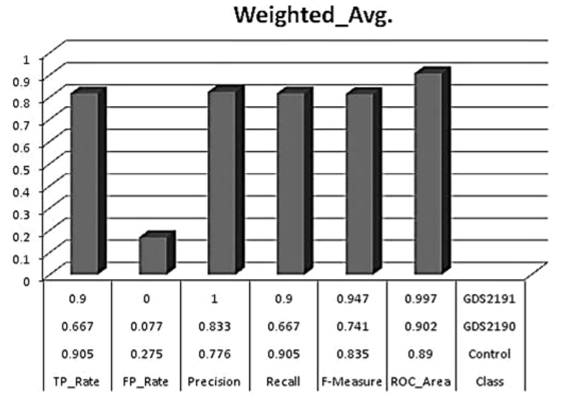
2.4 Biological Enrichment

We employed our newly developed prediction-based Bayesian network analysis to find molecular processes and pathways that are significant predictor of phenotype. To determine molecular processes and pathways we used Gene Ontology (GO) and Kyoto Encyclopaedia of Genes and Genomes (KEGG). See Table 2.

3 RESULTS

GEO DataSets (GDS) on the Affymetrix platform[17] related to Bipolar Disorder (Table S-1) were merged to form a set of 40 infected patients and 42 control patients. This set of samples was then used to construct Bayesian prognostic model and perform external cross validation on the results, for predicting bipolar disorder disease genes.

Our unique contribution lies in validating the multi-net prognostic model through a data-driven approach by calculating the Area Under Receiver Operating Characteristic (Bewick et al., 2004) (AUROC) through External cross-validation(Braga-Neto and Dougherty, 2005), (Ambrosie and McLachlan, 2002) process that corrects the bias induced through the feature selection procedure(Ambrosie and McLachlan, 2002) (see Materials and Methods for more detail). Prediction based enrichment analysis (Harris et al., 2004) was then used for the shared-feature gene set to reveal pathways significant to Bipolar Disorder outcomes(Kanehisa and Goto, 2000), (Watford et al., 2004). The computed significant common-feature genes for bipolar-disorder (Beynon et al., 2009), (Schiffer, 2007), (Benazzi, 2007), (Morriss et al., 2007), (Sachs, 2007) related, from the results of external cross validation are shown in Table 1. Enrichment analysis is shown in Table 2.



0.9	0	1	0.9	0.947	0.997	GDS2191
0.667	0.077	0.833	0.667	0.741	0.902	GDS2190
0.905	0.275	0.776	0.905	0.835	0.89	Control
TP_Rate	FP_Rate	Precision	Recall	F-Measure	ROC_Area	Class

Figure 3: The prognostic accuracies of computed significant common-feature genes with average AUROC - 0.907.

3.1 Result Analysis

The probability of correctly classified Instances and errors after external cross validation showed that the model outperformed well in predicting the disease state genes from fewer samples by integrating common controls via the multi-nets, with an AUROC of 0.907 (as plotted in Figure 4).

The six genes found responsible for bipolar disorder are:

3.1.1 ADH5

Alcohol dehydrogenase class-3 is an enzyme that in humans is encoded by the *ADH5* gene. This gene encodes glutathione-dependent formaldehyde dehydrogenase or class III alcohol dehydrogenase chi subunit, which is a member of the alcohol dehydrogenase family. Members of this family metabolize a wide variety of substrates, including ethanol, retinol, other aliphatic alcohols, hydroxysteroids, and lipid peroxidation products. This enzyme is an important component of cellular metabolism for the elimination of formaldehyde, a potent irritant and sensitizing agent that causes lacrymation, rhinitis, pharyngitis, and contact dermatitis. This gene has shown its influence on Brain and Brain GAMG Cancer. Hence, studies are further focussed on these relations for validation through medical test.

3.1.2 MCL1

MCL1 (myeloid cell leukemia sequence 1 (BCL2-related)) is a protein-coding gene. This gene encodes an anti-apoptotic protein. Alternative splicing results in multiple transcript variants. The longest gene product (isoform 1) enhances cell survival by inhibiting apoptosis while the alternatively spliced shorter gene products (isoform 2 and isoform 3) promote apoptosis and are death-inducing. Diseases associated with

MCL1 include cholangiocarcinoma, and t-cell leukemia, and among its related super-

pathways are Apoptosis and Immune response IL-22 signaling pathway. GO annotations related to this gene include protein channel activity and protein heterodimerization activity which reveal abnormal behaviour in bipolar patients.

3.1.3 PDE1A

Cyclic nucleotide phosphodiesterases (PDEs) play a role in signal transduction by regulating intracellular cyclic nucleotide concentrations through hydrolysis of cAMP and/or cGMP to their respective nucleoside 5-prime monophosphates. Members of the PDE1 family, such asPDE1A, are Ca(2+)/calmodulin (see CALM1; MIM 114180)-dependent PDEs (CaM-PDEs) that are activated by calmodulin in the presence of Ca(2+). While the PDE1A protein expression data from MOPED reveals the interrelation of this gene with brain and thus with bipolar, PDE1A is further validated through medical test for thorough confirmation of its presence in bipolar disorder patients.

3.1.4 ASPH

ASPH (aspartate beta-hydroxylase) is a protein-coding gene. Diseases associated with **ASPH** include Brain GAMG Cancer, regular astigmatism, and catecholaminergic polymorphic ventricular tachycardia. GO annotations related to this gene include electron carrier activity and calcium ion binding. An important paralog of this gene is ASPHD2. This gene is thought to play an important role in calcium homeostasis. The gene is expressed from two promoters and undergoes extensive alternative splicing.

3.1.5 NTM

NTM (neurotrimin) is a protein-coding gene in brain. Diseases associated with NTM include crimean-congo haemorrhagic fever, and olivopontocerebellar atrophy. GO annotations related to this gene include protein binding shown in Table 2.

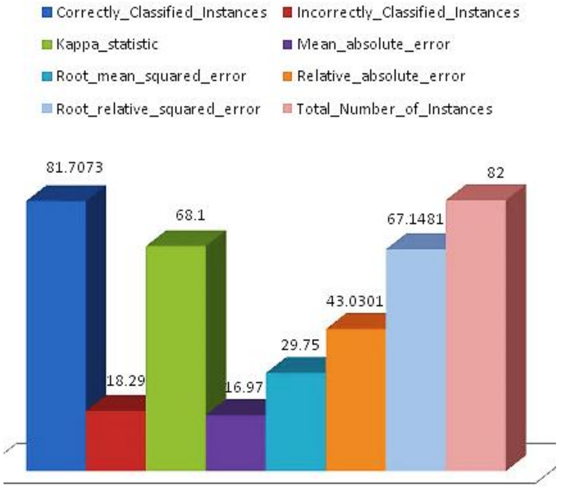


Figure 4: The plot of correctly classified instances and incorrectly classified instances Vs Total Number of Instances and errors after External Cross validation.

3.1.6 C8ORF44

C8ORF44 is chromosome 8 open reading frame 44 related to brain and hence also found to be associated with bipolar disorder with an AUROC of 0.907

4 DISCUSSION

AUROC provides an objective metric for quantifying predictor performance. An AUROC of 0.7 to 0.8 is considered “fair,” from 0.8 to 0.9 is considered “good”, and from 0.9 to 1.0 is considered “excellent” (Caruana and Niculescu-Mizil, 2006). The multi-net classifier for Bipolar disorder across classes of patients achieved ‘excellent’ performance. However, the singly-structured model for Bipolar disorder, whose structures were fixed across all patients, only achieved ‘good’ performance. These results indicate the power of this experiment-integration framework as that:

(1) Merging controls in related experiments results in a larger control group increasing the power of association in learning and,

(2) The External cross validation improves the results accuracy and determines the best genes responsible for the disease.

4.1 Newly Implicated Genes and Chromosomal Loci

Using this integrative approach, new genes were discovered by testing Bipolar disorder infected patients from many experiments against a larger set of merged controls. The six genes MCL1(Gene MCL1), PDE1A(Gene PDE1A), ADH5(Gene ADH5), ASPH(Gene ASPH), C8ORF44(Gene C8ORF44) and NTM(Gene NTM) (Table 1, Figure 5) should be studied in the future context of Bipolar disorder as these studies can shed some light on these relationships and the functions of these genes and gene products.

Analysis of these genes showed that five significant chromosomal regions - Chromosomes 1, 2, 4, 8 and 11 (Figure 6) were significant in Bipolar disorder. Because gene expression in nearby chromosomal loci is strongly related, these significant regions are of medical interest (Takizawa et al., 2008).

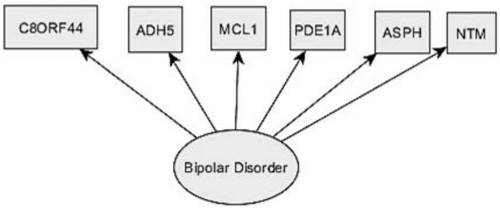


Figure 5: Common-feature genes responsible for Bipolar disorder resulted from External Cross validation with an accuracy of 90.7%

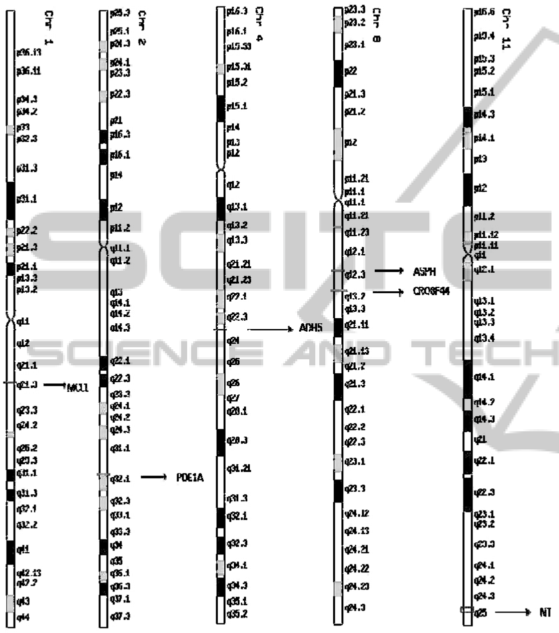


Figure 6: Analysis of genes from all the multi-net models showed that five significant chromosomal regions on Chromosomes 1, 2, 4, 8 and 11 were significant in Bipolar disorder due to the presence of the Genes MCL1, PDE1A, ADH5, ASPH, CRO8F44 and NTM in them.

4.2 Enrichment Analysis and Features in Bipolar Disorder Genes

Enrichment analysis of the shared-feature set (in Table 1) reveal GO and KEGG biological concepts related to bipolar disorder disease. Many of the biological pathways with p-value <=0.05 have shown to be associated with Bipolar Disorder genes. Peptidyl-amino acid modification is the alteration of an amino acid residue in a peptide which lowers in bipolar disorder infected patients. Electron carrier activity is a molecular entity that serves as an electron acceptor and electron donor in an electron transport system, present in ADH5 and ASPH. Furthermore, Bipolar disorder was also found to be associated with neoplasia (in Table 2) which needs a further study.

The proteins with certain p-value in Table 3 specify the bipolar disease state in six genes – MCL1, PDE1A, ADH5, C8ORF44, NTM, ASPH.

Table 1: The computed significant common-feature genes for bipolar disorder related, from the results of external cross-validation.

Gene Symbol	Gene ID	Organism	Gene Name
MCL1	4170	Homo sapiens	myeloid cell leukemia sequence 1 (BCL2-related)
PDE1A	5136	Homo sapiens	phosphodiesterase 1A, calmodulin-dependent
ADH5	128	Homo sapiens	alcohol dehydrogenase 5 (class III), chi polypeptide, pseudogene 4; alcohol dehydrogenase 5 (class III), chi polypeptide
C8ORF44	56260	Homo sapiens	chromosome 8 open reading frame 44
ASPH	444	Homo sapiens	aspartate beta-hydroxylase
NTM	50863	Homo sapiens	Neurotrimin

Table 2: Enrichment analyses of the shared-feature set reveal GO and KEGG biological concepts related to Bipolar Disorder.

Biological Concept	*p*-value
GO:0018193~peptidyl-amino acid modification(ADH5, ASPH)	0.0451
GO:0009055~electron carrier activity (ADH5, ASPH)	0.0502
21275:lung_normal_3rd (ADH5, NTM)	0.0234
519:pancrea_neoplasia_3rd (ADH5, ASPH)	0.0277
38125:esophagu_neoplasia_3rd (ADH5, ASPH)	0.0473
26751: lymph node_neoplasia_3rd (ADH5, ASPH)	0.0485
BM-CD105+Endothelial_3rd (MCL1, PDE1A, ASPH, C8ORF44, NTM)	0.0229
Adrenal Cortex_3rd (MCL1, PDE1A, ADH5, ASPH)	0.0366

Table 3: Proteins in Bipolar genes that specify the disease.

Proteins	Genes	p-Value
HFH3	MCL1, PDE1A, ADH5, ASPH, C8ORF44, NTM	0.0044
SRY	MCL1, PDE1A, ADH5, ASPH, C8ORF44, NTM	0.0051
FREAC7	MCL1, PDE1A, ADH5, ASPH, C8ORF44, NTM	0.0110
LUN1	MCL1, PDE1A, ADH5, ASPH, C8ORF44, NTM	0.0129
FOXD3	PDE1A, ADH5, ASPH, C8ORF44, NTM	0.0244

4.3 Unique Contribution and Future Work

This study presents a completely data-driven approach to integrate phenotypic content from multiple experiments, to discover significant bipolar disorder-related genes and biological pathways, and to verify their importance without resorting to *a priori* information bases. External cross validation is utilized as an integrative tool to construct the best classifier for disease analysis and evaluate it using best evaluation method. The multi-net model, used for the first time in disease analysis with external cross validation, showed huge improvements over singly-structured models in predicting Bipolar disorder state from gene expression. The results demonstrate the involvement of six new genes and five chromosomal regions in bipolar disorder that should be targeted in future clinical studies. In the future, we anticipate that this novel, data-driven and prediction-based integrative approach will enable the discovery of the genetic basis of many diseases.

5 CONCLUSIONS

Using this integrative approach, 6 Genes - MCL1, PDE1A, ADH5, ASPH, C80RF44 and NTM were identified as responsible for Bipolar disorder in humans. Future studies can shed some light on these relationships and the functions of these genes and gene products. Results indicated that the Multi-netmodel with external cross validation 'outperformed' singly-connected ones in predicting Bipolar disorder disease state genes from gene expression with an 'excellent' AUROC of 0.907.

We are also further working on implementing this design on other pathologies for advanced prevention and cure of diseases like Cancer, AIDS etc.

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