

Whole Genome Association Study of Bipolar Disorder

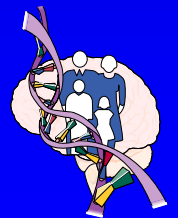
John R. Kelsoe

Laboratory of Psychiatric Genomics

Department of Psychiatry

University of California

San Diego



Laboratory of
Psychiatric Genomics

Bipolar Disorder

Manic Depressive Illness

- Mania

- Elevated or irritable mood
- Grandiosity
- Decreased need for sleep
- Increased or pressured speech
- Flight of ideas or racing thoughts
- Increased goal directed activity
- Risk taking
- Functional impairment

- Depression

- Low mood
- Loss of interest or pleasure
- Change in appetite or weight
- Insomnia or hypersomnia
- Fatigue
- Feelings of worthlessness
- Impaired memory or concentration
- Suicidality
- Clinically significant distress or impairment

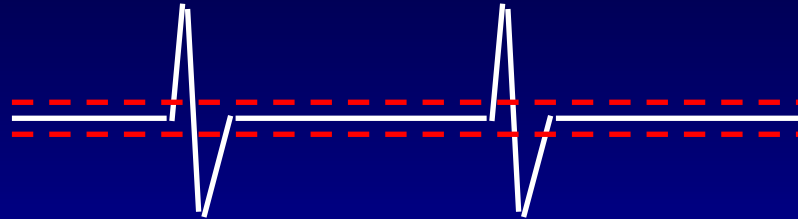
1-2% population prevalence worldwide

Clinical Features of Bipolar Disorder

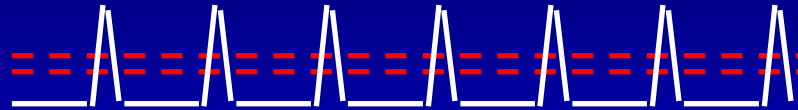
- Age of onset early twenties
- 1% prevalence
- Male and Female prevalence equal
 - M:F = 1:3 in unipolar disorder
- 60-80% of cases begin with mania
- 4-18% of those with depression later have mania
- Stable features
 - Seasonality (Seasonal Affective Disorder)
 - Psychosis
 - Rapid cycling
- Related syndromes and disorders
 - Mixed states
 - Schizoaffective disorder
 - Substance abuse and alcoholism

Bipolar Phenotypes

Bipolar I



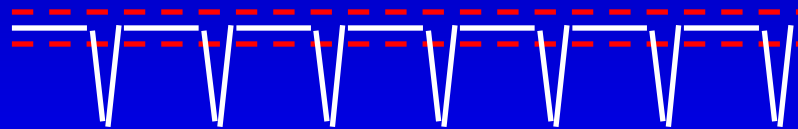
Bipolar II



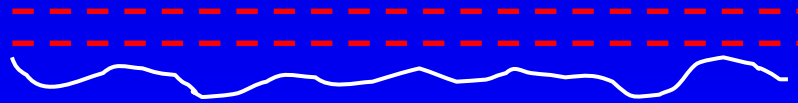
Cyclothymia



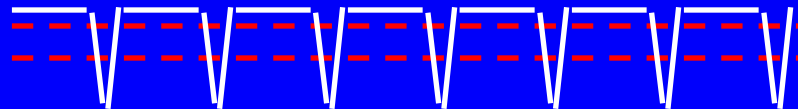
Unipolar



Dysthymia



Unipolar-
Hyperthymic



Affective Illness In First Degree Relatives

Bipolar Probands

	Relatives at Risk	Morbid Risk (%) BP	UP
Perris, 1966	627	10.2	0.5
Winokur and Clayton, 1967	167	10.2	20.4
Mendlewicz and Rainer, 1974	606	17.7	22.4
Goetzl et al., 1974	212	2.8	13.7
Helzer and Winokur, 1974	151	4.6	10.6
Gershon et al., 1975	341	3.8	6.8
James and Chapman, 1975	239	6.4	13.2
Johnson and Leeman, 1977	126	15.5	19.8
Petterson, 1977	472	3.6	7.2
Smeraldi et al., 1977	172	5.8	7.1
Trzeblatowska-Trzeciak		11.4	0.0
Angst, 1980	400	2.5	7.0
Dunner, Go, and Fieve, 1980	1199	4.2	8.2
Taylor, Abrams, and Hayman, 1980	600	4.8	4.2
Gershon et al., 1982	598	8.0	14.9
Tsuang et al., 1985	608	3.9	9.1
Rice et al., 1987	557	5.7	23.0
Total	7364	6.8	10.4

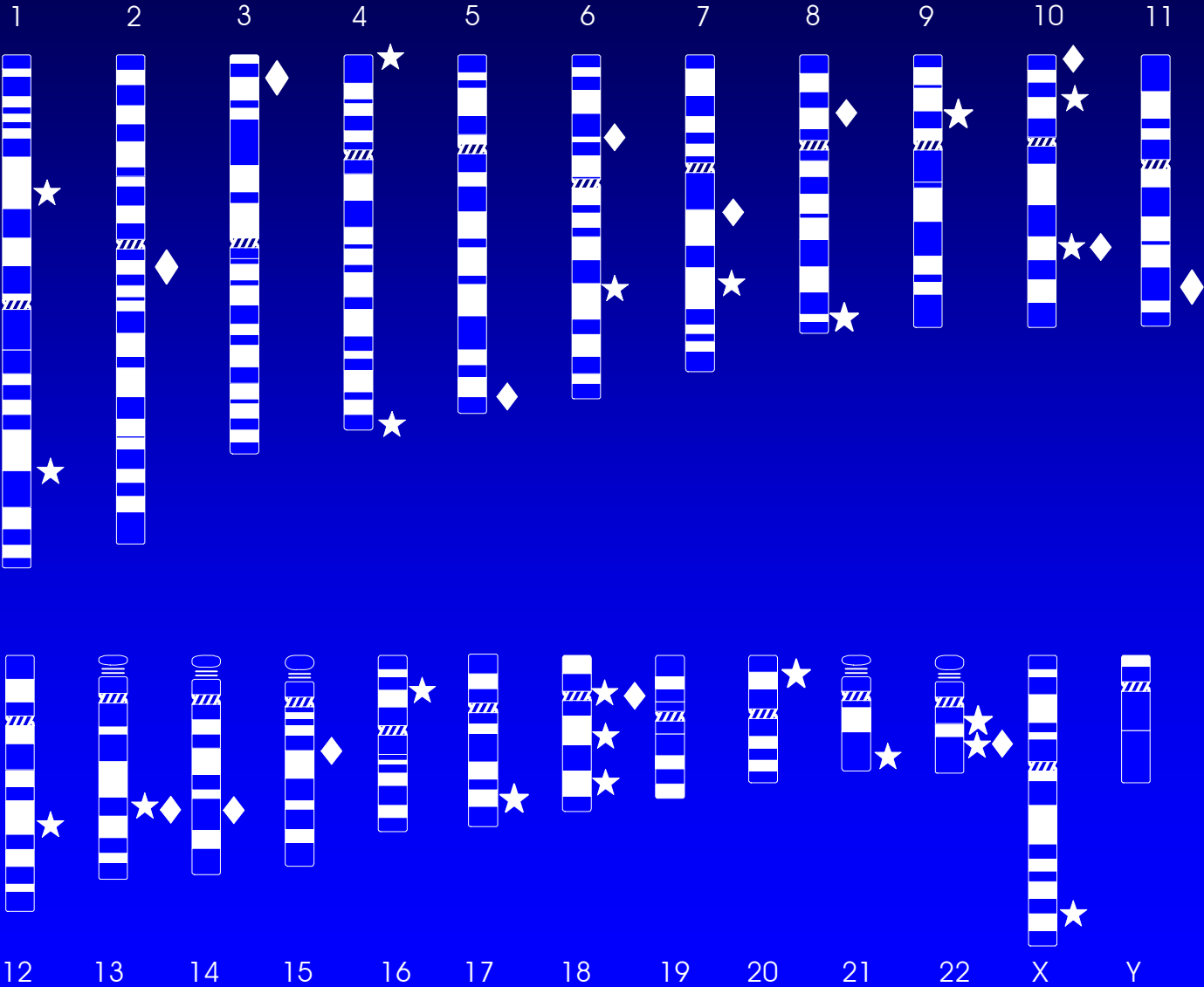
Twin Studies of Affective Illness

Study	Monozygotic		Dizygotic	
	Concordance	(%)	Concordance	(%)
Luxenberger, 1930	3/4	75.0	0/13	0.0
Rosanoff et al., 1935	16/23	69.6	11/67	16.4
Slater, 1953	4/7	57.1	4/17	23.5
Kallman, 1954	25/27	92.6	13/55	23.6
Harvald and Hauge, 1965	10/15	66.7	2/40	5.0
Allen et al., 1974	5/15	33.3	0/34	0.0
Bertelsen, 1979	32/55	58.3	9/52	17.3
TOTAL	95/146	65.0	39/278	14.0

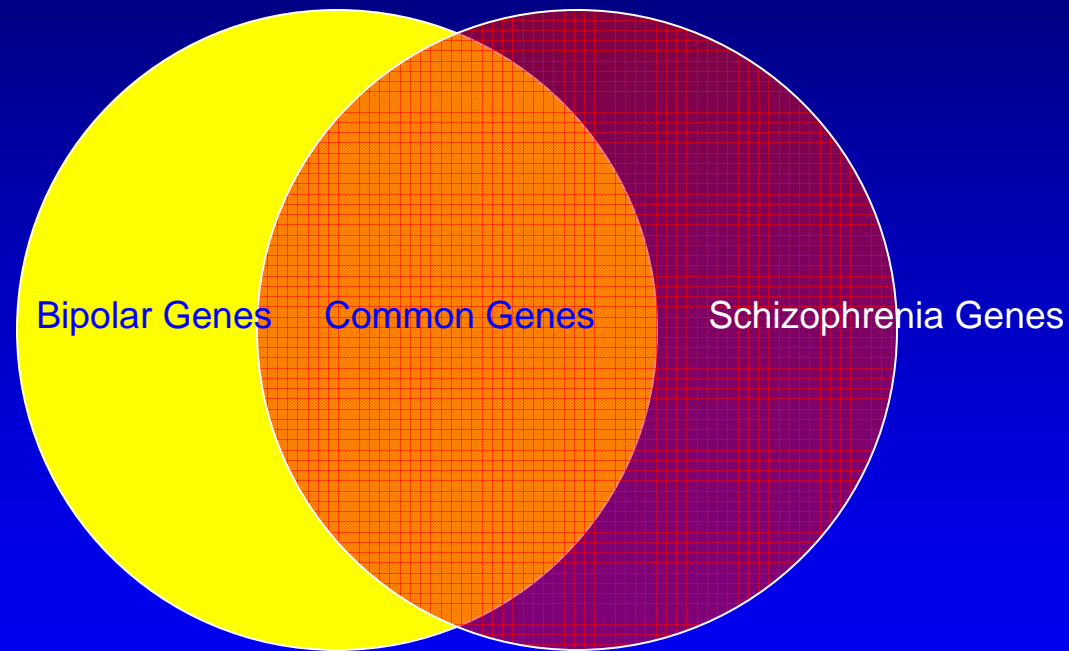
Linkage hotspots for bipolar disorder and schizophrenia

★ Bipolar

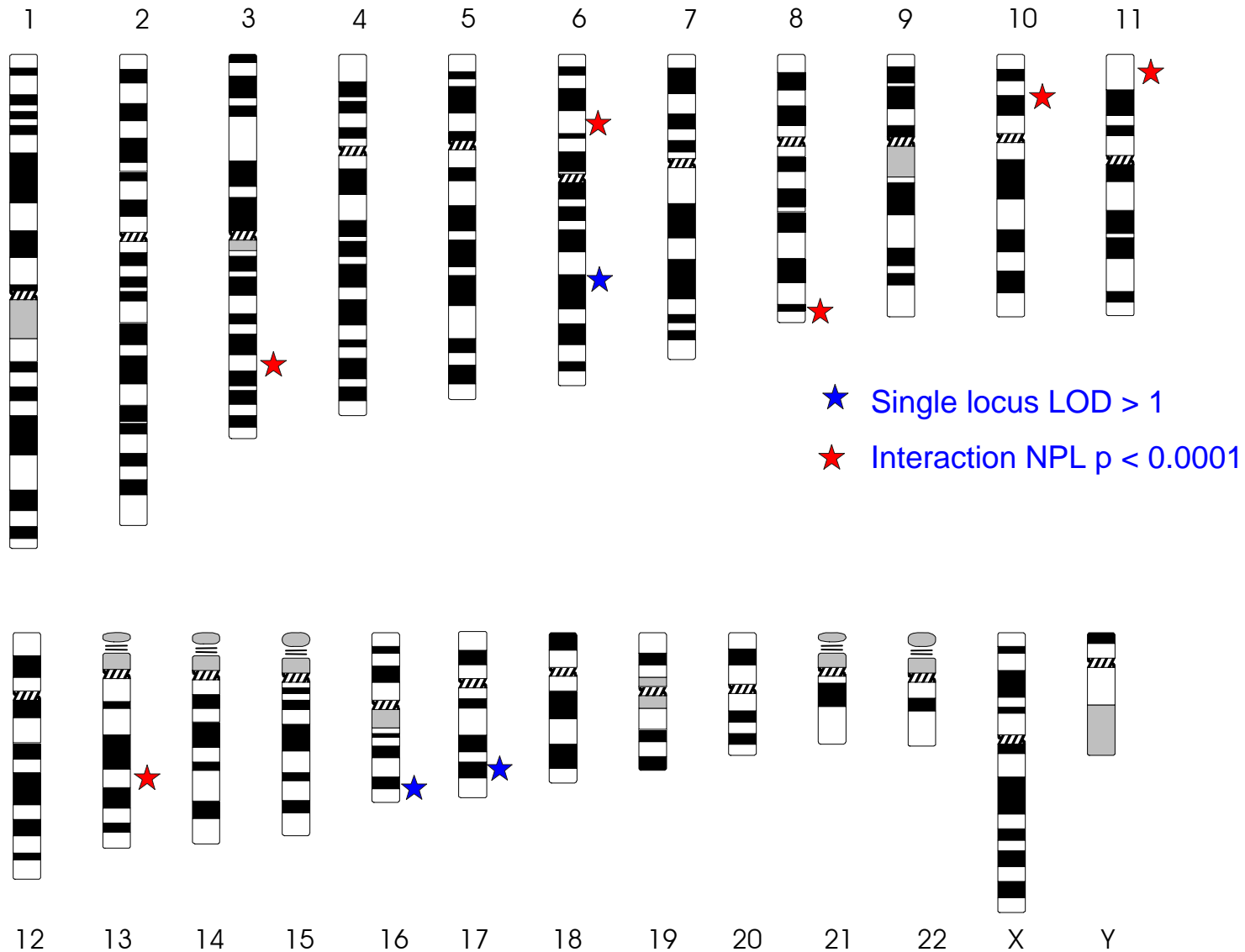
◆ Schizophrenia



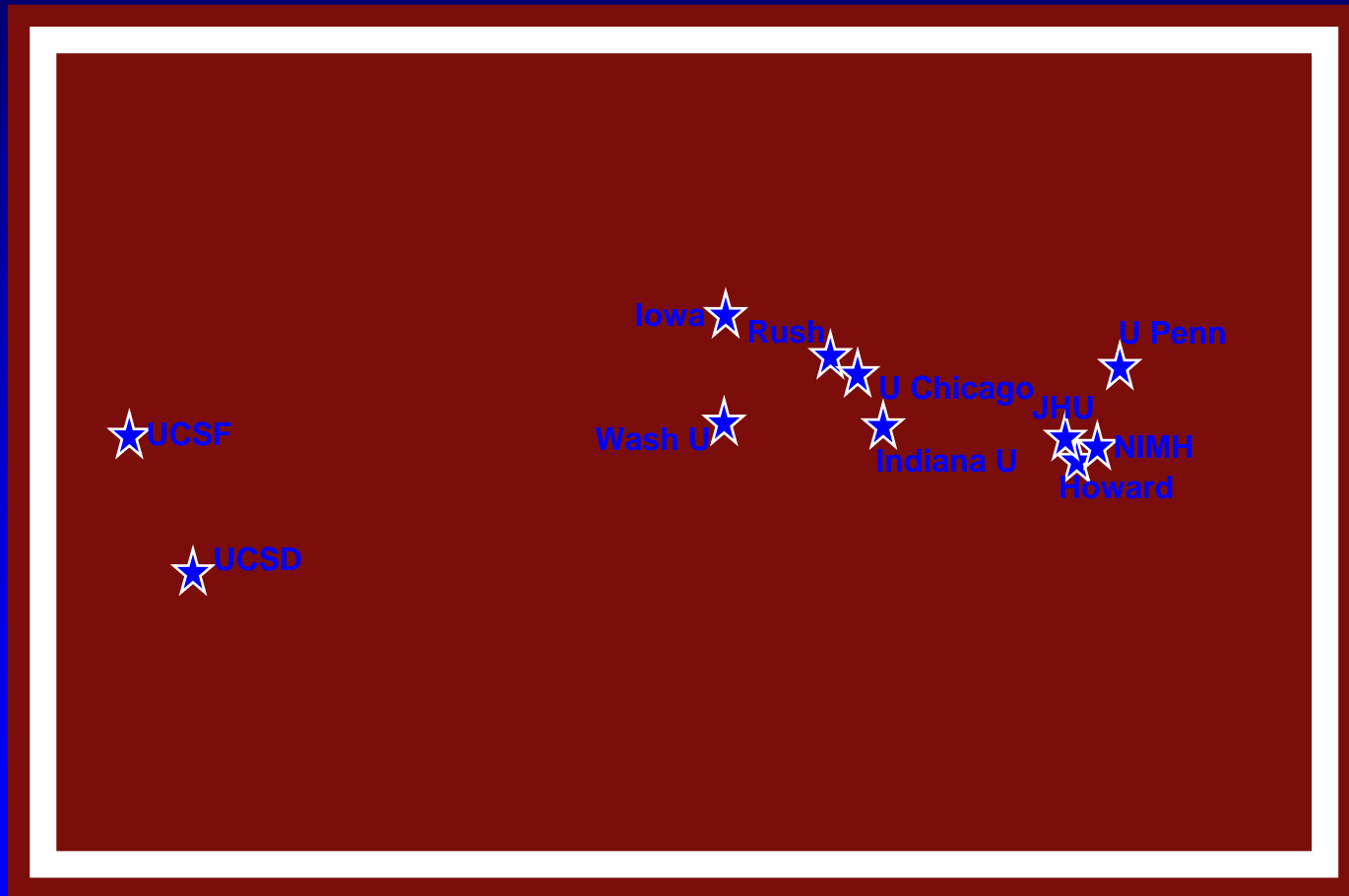
Are Bipolar Disorder and Schizophrenia Different?



Linkage Peaks for Bipolar Disorder Wave 1-4 Combined Sample



NIMH Genetics Initiative for Bipolar Disorder Consortium Sites



Waves 1 & 2

Waves 3 & 4

Wave 5

NIMH Genetics Initiative for Bipolar Disorder

Wave	Sites	Ascertainment	Families	Subjects	Subjects with DNA
Wave 1	4 sites	BPI probands	97	758	571
Wave 2			56	437	358
Wave 3	9 sites	BPI-BPI sib pairs	218	1581	995
Wave 4			275	1583	1057
Wave 5	11 sites	BPI unrelated cases Goal 5,500		2142 total 1861 EA 281 AA 388 parents	2142
Total			646	6501	5123

Subject Ascertainment

- 11 sites nationwide
- Project-wide web site
- Site specific web sites
- Hospital based
- Outpatient clinics
- Patient support groups
- Local psychiatrists

Phenotypic Assessment Diagnosis

- Diagnostic Interview for Genetic Studies (DIGS) 3.0
 - Interviewer administered survey
 - Both face-to-face and telephonic
 - Large dataset – 2400 variables
 - Detailed assessment of mood disorder
 - Survey of wide range of psychiatric syndromes
 - Reliability tested
- Final Best Estimate Diagnostic Procedure
 - DIGS
 - Medical records
 - Other family informants
 - DSM-IV and other systems

Phenotypic Assessment Rating Scales

- Rating scales
 - TEMPS-A Affective Temperament
 - TCI-125 Temperament
 - BALM Circadian rhythmicity
 - Childhood Life Events Scale
 - Lifetime History of Aggression
 - Visual Analog Scale State rating of mood
 - Wender Questionnaire Childhood ADHD
 - Zuckerman-Kuhlman Personality questionnaire
 - Questionnaire about Genetic Risk Knowledge of genetic risks

Case Selection

- BPI
- Family history
- Primarily EA cases from wave 1-4
- Supplement with wave 5
- Matching Criteria
 - Ethnicity
 - Gender

Control Selection

- Collected by Schizophrenia Consortium (Gejman)
 - Random digit dialing
- Shared samples and genotyping
- Exclude subjects with histories of
 - Major Depression
 - Psychosis
 - Bipolar disorder or schizophrenia
- Matching Criteria
 - Ethnicity
 - Gender

Case Control Matching

	Cases	Controls
N	1000	1000
Ethnicity (%)		
Northern Europe	52	59
Western Europe	37	32
Eastern Europe	7	7
Southern Europe	4	3
Age (yrs)	42.3	53.6
Gender (% male)	51.8	52.3
Marital Status (% married)	44	69
Education	15 yrs	44% college degree

Site Distribution of Cases

<u>Site</u>	<u>COUNT</u>	<u>PERCENT</u>
Indiana U	150	15
Wash U	184	18.4
Hopkins	201	20.1
NIMH	162	16.2
U Penn	77	7.7
UC Irvine	32	3.2
Iowa	46	4.6
U Chicago	71	7.1
UC San Diego	46	4.6
Rush	86	8.6
UC San Francisco	25	2.5
Howard	1	0.1
Total	1000	100

Two Stage Design

GAIN

Affy 500K or 1M SNP Chip
Cases: 1000 BPI EA, 300 AA BPI
Controls: 1000 EA, 300 AA



Selection of positive regions for followup

Significance
Clustering
Genes, regions or pathways w prior evidence



Additional genotyping in second sample

25,000 SNPs old and new
1000 BPI cases / 1000 controls
MIP – TGEN
Sequenom – U Indiana
SNPlex – UCSD
Illumina - NIMH

Putative Genetic Subphenotypes

- Psychosis (64%)
- Age of onset (19yo)
- Dysphoric / Irritable mania
- Co-morbid anxiety disorders (24% PD)
- Co-morbid substance abuse (~40%)
- Circadian abnormalities
- Suicidality
- Episode frequency
- Polarity at onset

Collaborators

- Indiana U.
 - John Nurnberger
 - Howard Edenberg
 - Tatiana Foroud
 - Eric Meyer
- Johns Hopkins
 - Raymond DePaulo
 - James Potash
 - Dean McKinnon
 - David Cutler
- NIMH
 - Francis McMahon
- Washington U.
 - Ted Reich
 - John Rice
- U Chicago
 - Elliot Gershon
 - Judy Badner
- UCSD
 - John Kelsoe
 - Nik Schork
- UCI -> UCSF
 - William Byerley
- U Iowa
 - William Coryell
- Rush Presbyterian
 - William Scheftner
- Howard U
 - William Lawson
- U Pennsylvania
 - Wade Berrettini
- U Michigan
 - Melvin McInnis
- TGEN
 - David Craig
 - Dietrich Stephan