Genetics and Neurobiology of Mood Disorders

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Disclosures

- Investigator for Janssen on high risk studies for bipolar disorder

Lifetime Risk for Major Affective Disorder in Different Groups

Controls	Relatives of UP	Relatives of BP	Relatives of SA	Children of two ill parents	Identical twin ill
7%	20%	25%	40%	50%+	65%

Nurnberger J, in Strakowski S, The Bipolar Brain, 2012

Lifetime Risk for Bipolar Disorder in Different Groups

Controls	Relatives of UP	Relatives of BP	Relatives of SA	Identical twin ill
0.5-1%	3%	8%	17%	80%

Nurnberger J, in Strakowski S, The Bipolar Brain, 2012

LIFETIME PREVALENCE OF AFFECTIVE ILLNESS IN FIRST-DEGREE RELATIVES OF PATIENTS AND CONTROLS

	Number at Risk	Morbid Risk (%)	
		Bipolar	Unipolar
Bipolar Probands			
Perris 1966	627	10.2	0.5
Winokur and Clayton 1967	167	10.2	20.4
Goetzl et al. 1974	212	2.8	13.7
Helzer and Winokur 1974	151	4.6	10.6
Mendlewicz and Rainer 1974	606	17.7	22.4
James and Chapman 1975	239	6.4	13.2
Gershon et al. 1975b	341	3.8	8.7
Smeraldi et al. 1977	172	5.8	7.1
Johnson and Leeman 1977	126	15.5	19.8
Pettersen 1977	472	3.6	7.2
Angst et al. 1979, 1980	401	2.5	7.0
Taylor et al. 1980	601	4.8	4.2
Gershon et al. 1981b, 1982	598 (572)	8.0	14.9
Rice et al. 1987	567	10.4	23.1

LIFETIME PREVALENCE OF AFFECTIVE ILLNESS IN FIRST-DEGREE RELATIVES OF PATIENTS AND CONTROLS

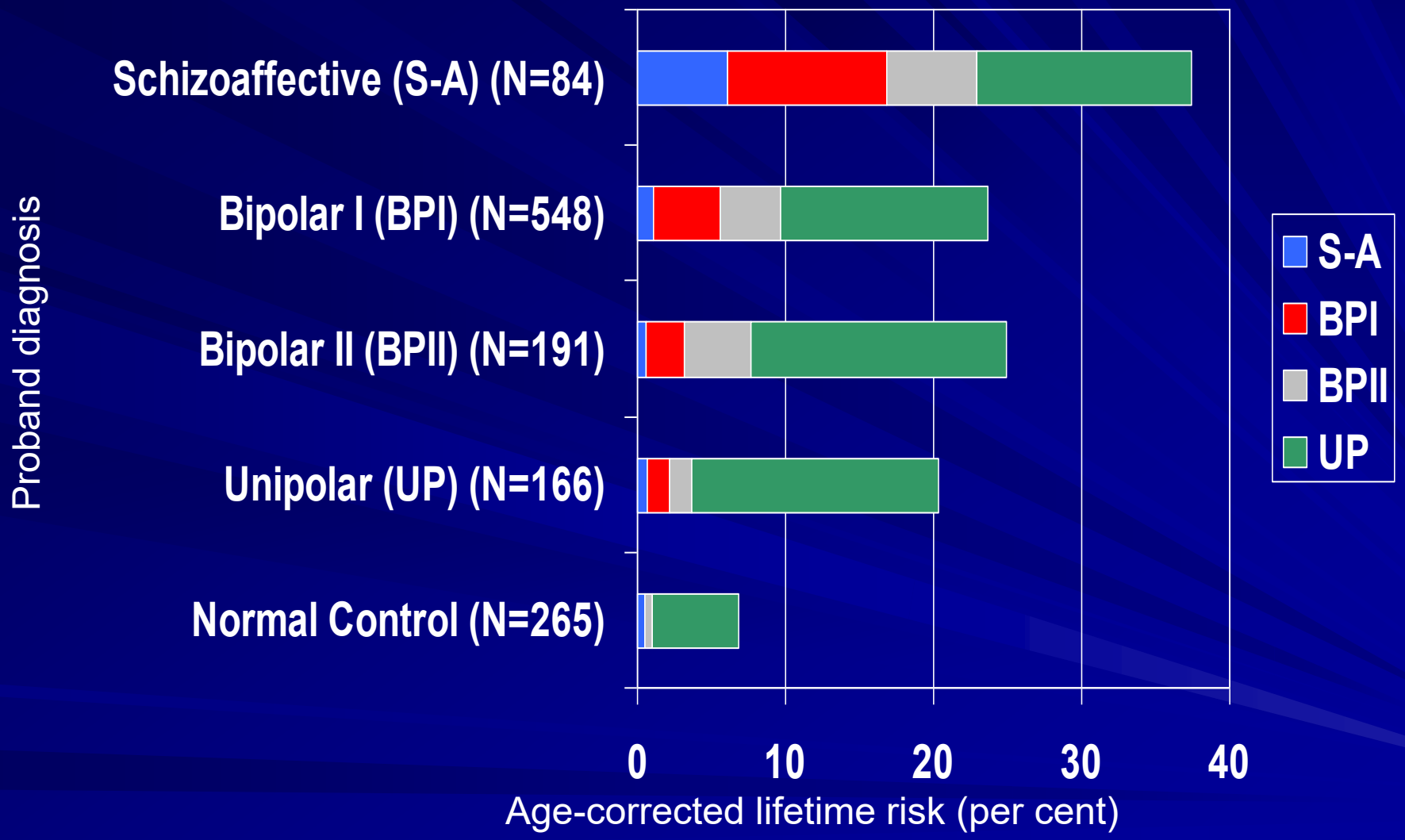
	Number at Risk	Morbid Risk (%)	
		Bipolar	Unipolar
Unipolar Probands			
Perris 1966	684	0.3	6.4
Gershon et al. 1975b	96	2.1	14.2
Smeraldi et al. 1977	185	0.6	8.0
Angst et al. 1979, 1980	766	0.1	5.9
Taylor et al. 1980	96	4.1	8.3
Weissman et al. 1984 (Severe)	242 (234)	2.1	17.5
Weissman et al. 1984 (Mild)	414 (396)	3.4	16.7
Gershon et al. 1981b, 1982	138 (133)	2.9	16.6
Rice et al. 1987	1176	5.4	28.6
Normal Probands			
Gershon et al. 1975b	518 (411)	0.2	0.7
Weissman et al. 1984	442 (427)	1.8	5.6
Gershon et al. 1981b, 1982	217 (208)	0.5	5.8

CONCORDANCE RATES FOR MAJOR AFFECTIVE DISORDER IN MONOZYGOTIC AND DIZYGOTIC TWINS

Study	Monozygotic Twins		Dizygotic Twins	
	Concordant Pairs / TOTAL PAIRS	Concordance (%)	Concordant Pairs / TOTAL PAIRS	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 & Hauge (1975)	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
Torgersen (1986)	14/37	37.8	8/65	12.3
Totals	109/183	59.6%	47/343	13.7%

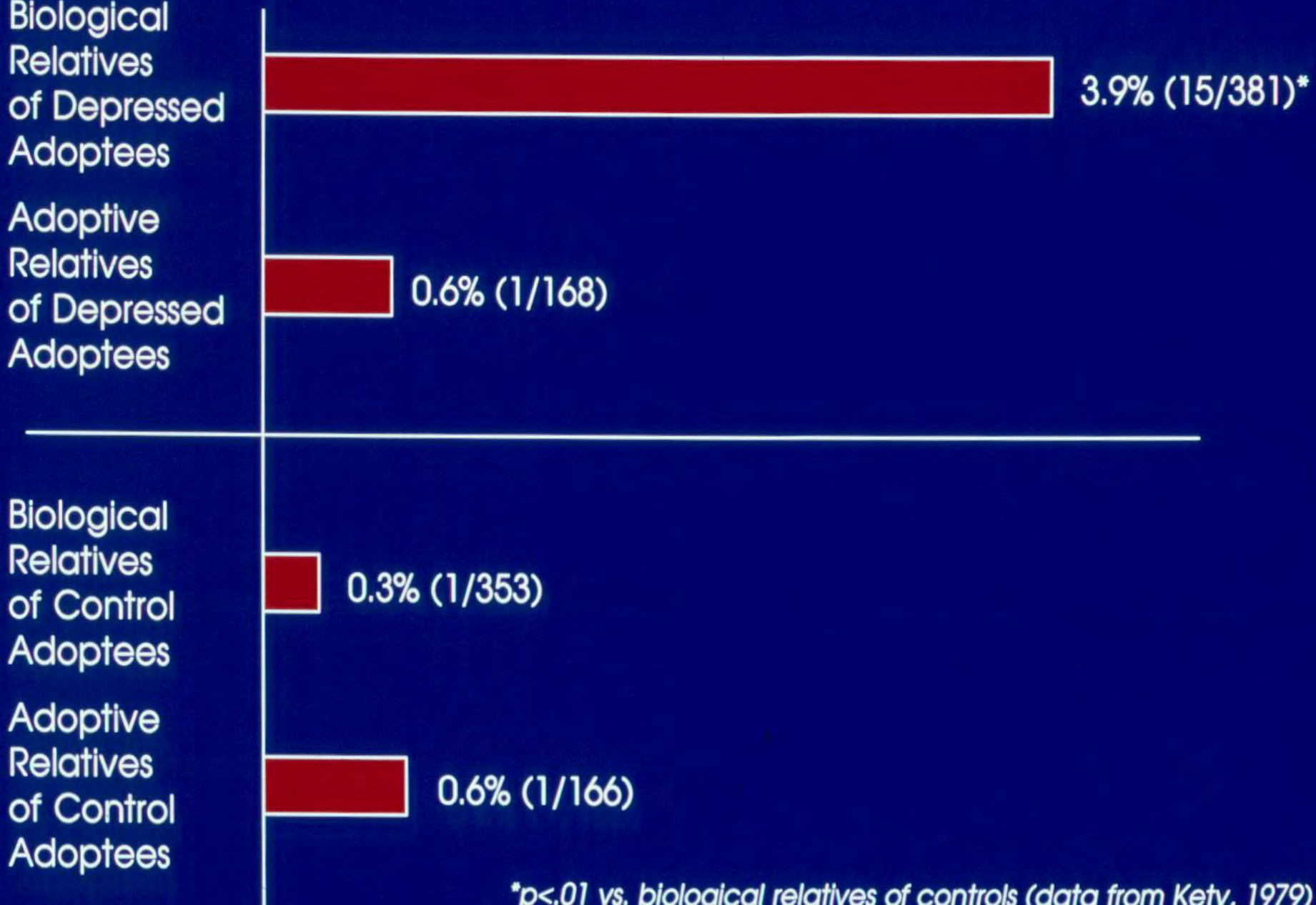
Genetic Epidemiology of Depression

- Family studies show RR of ~2.8 for MDD and ~1.7 for BP in relatives of UP probands (Potash, 2012).
- RR for recurrent early-onset ~4-5 (Levinson et al, 2006).
- Heritability from a large twin study ~.38 (.42 in women and .29 in men) (Kendler et al, 2006).



Data from Gershon et al, 1982

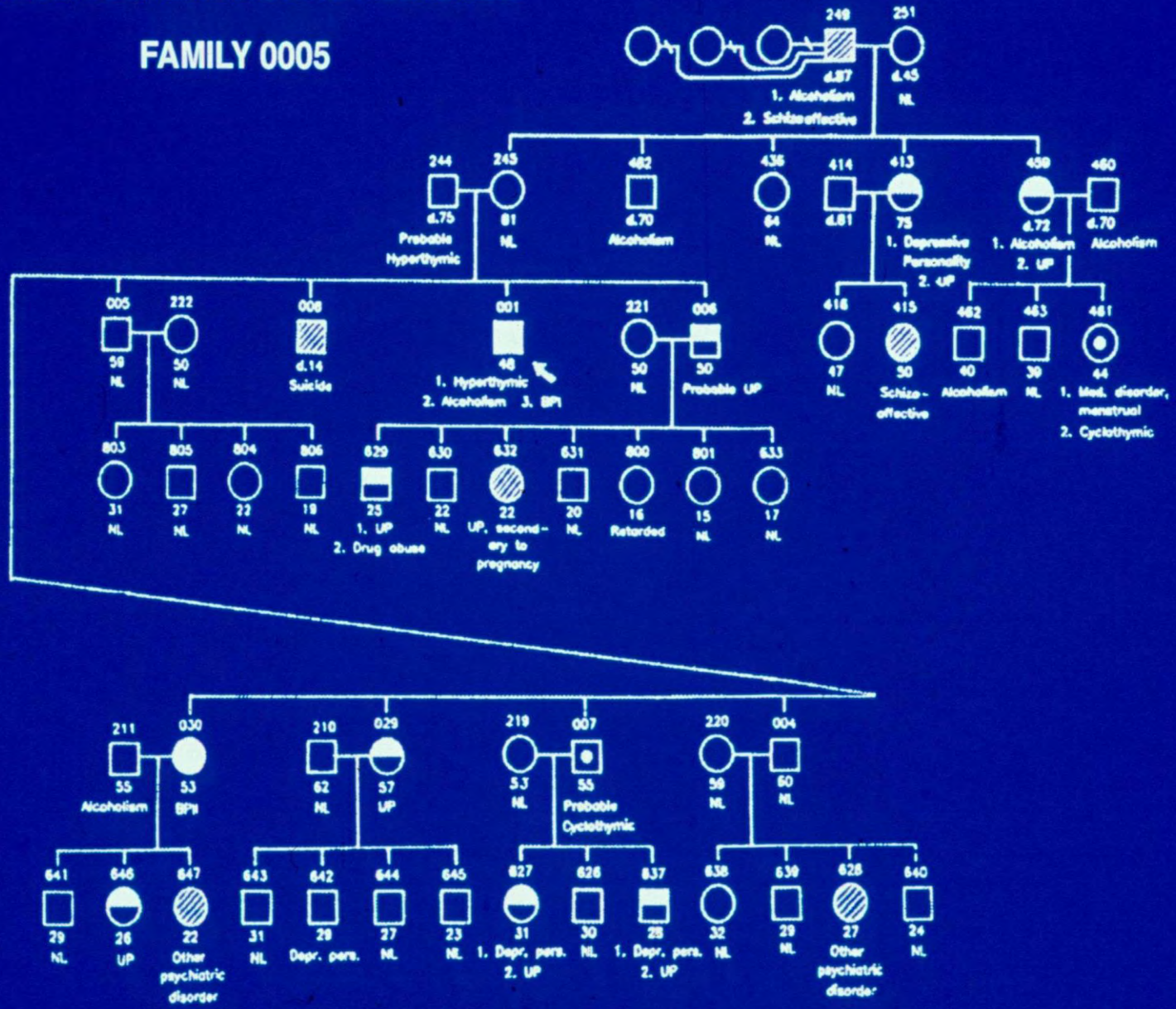
SUICIDE IN RELATIVES OF ADOPTEES WITH DEPRESSION



*p<.01 vs. biological relatives of controls (data from Kety, 1979)

A MULTIGENERATIONAL PEDIGREE

FAMILY 0005

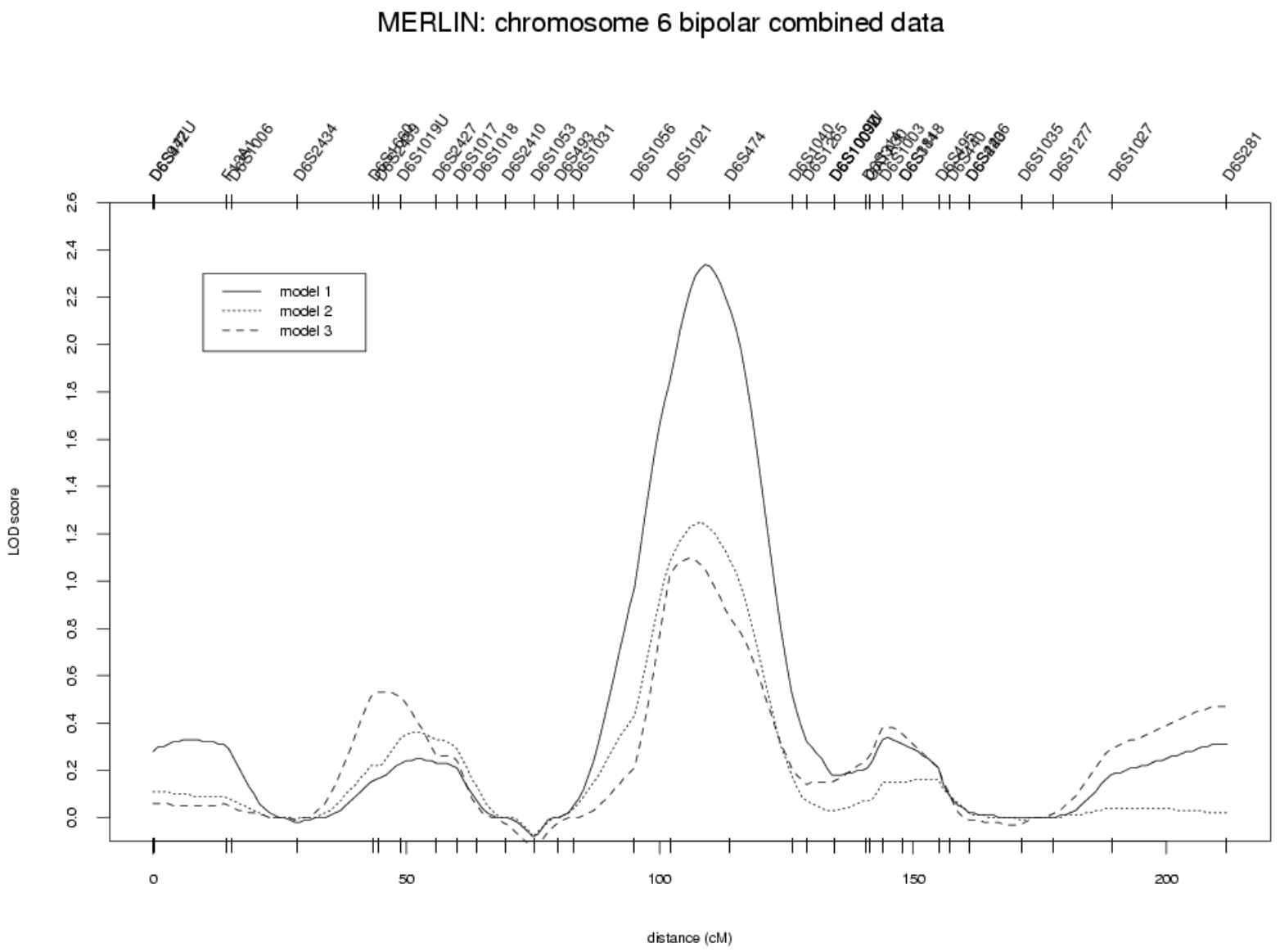


Genetics of common disease

- Resolving the genetics of a complex trait, or disease, is more difficult than that of a Mendelian trait.
- Typically, large samples of sib pairs are used for linkage studies.
- Large case/control samples are used for association studies.
- Genetic defects may be a combination of chromosomal anomalies (now including small copy number variants), rare variants (<1% frequency), and common variants.

Genetics of Common Disease (2)

- Genetic analysis by model-free methods
- Increased attention to epistasis
- Early successes: BRCA1 and 2, angiotensinogen for HPT, HLA and the insulin receptor for IDDM, calpain for NIDDM, genes related to asthma and inflammatory bowel disease, four genes related to rare forms of Alzheimer's, plus APoE related to common forms.
- Specific gene variants now reported and replicated in SZ, ALC, BP.
- All genes noted account for modest proportion of variance (generally < 0.1%)

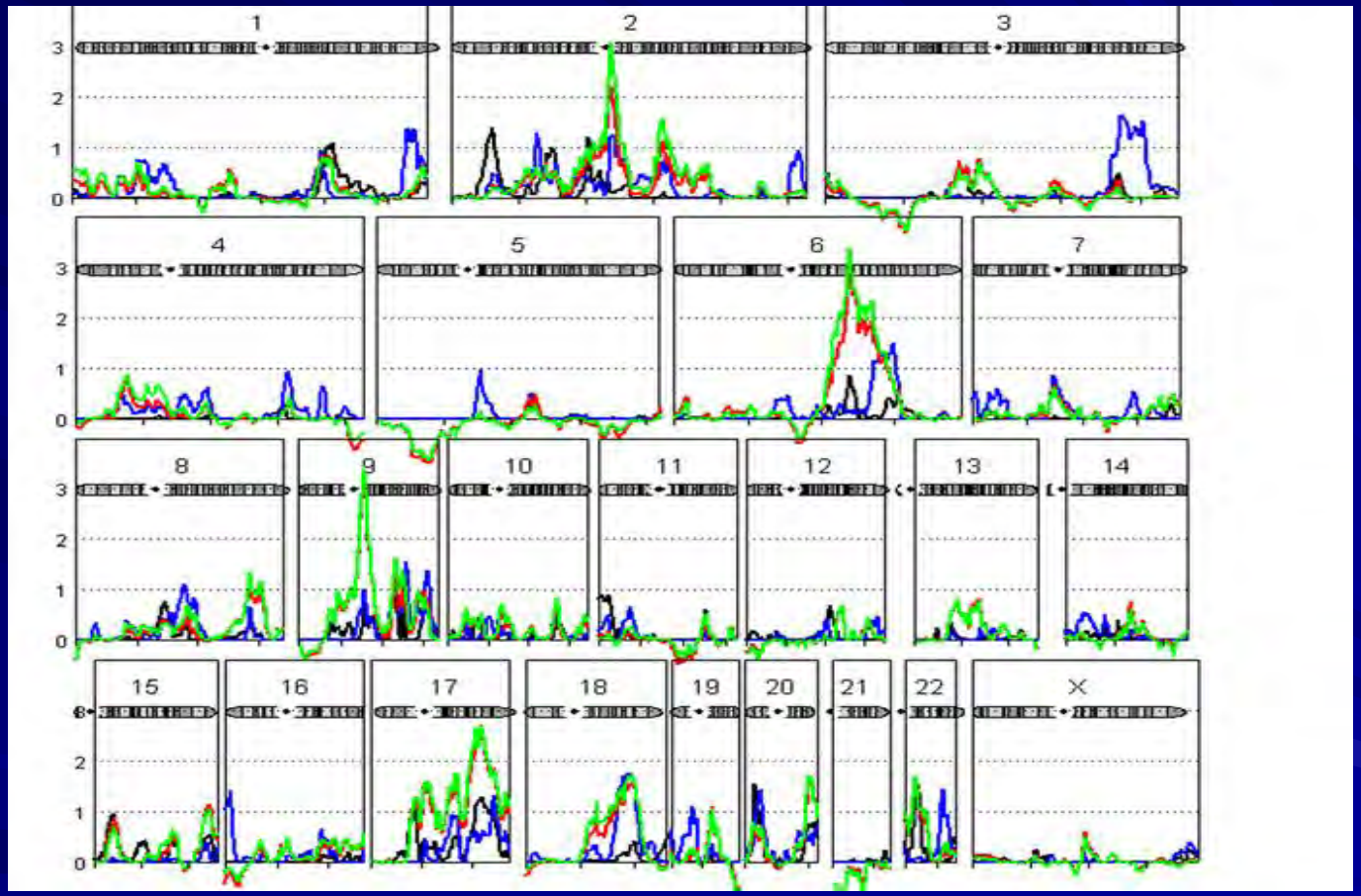


Dick et al, American Journal of Human Genetics, 2003

Linkage Studies in Bipolar Disorder

- Metaanalysis by McQueen et al, AJHG 2005 included 11 scans of 1067 pedigrees (5179 subjects) identifying 6q and 8q as areas of genomewide significance.
- Badner and Gershon metaanalysis identified 13q and 22q.
- Previous single studies meeting genomewide criteria identified 4p, 18p, 18q, and 22q.
- A large single sample analysis implicated 16p using a dominant model (Ross et al, 2008).
- A recent study of 972 pedigrees showed linkage at 6q21 and 9q21 (Badner et al, 2012).

Linkage analysis of BP from 972 pedigrees



Badner et al, 2012

Genome wide Association Studies (GWAS)

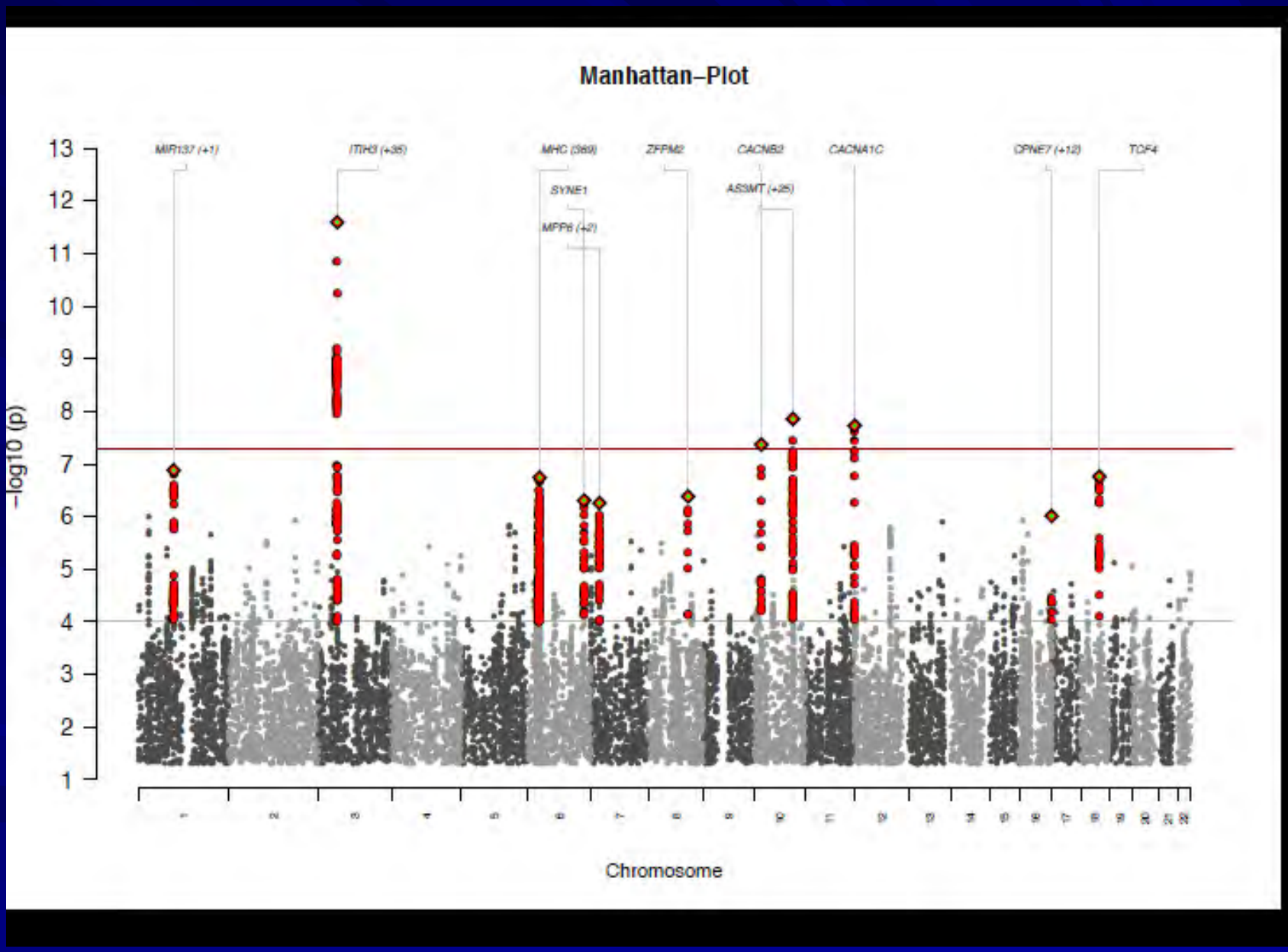
- Enables single nucleotide polymorphism (SNP) screening of the entire genome at intervals of 5-50 Kb.
- Requires sample sizes in the thousands (latest Bipolar collaborative sample >30,000 subjects).

NHGRI summary of significant genetic associations from GWAS studies, 1/17

http://www.ebi.ac.uk/gwas

GWAS in psychiatry

- At the last World Congress of Psychiatric Genetics, new gene variants associated with psychiatric disorders were reported, including >100 gene variants in Schizophrenia, >20 in Bipolar Disorder.
- All of these variants are associated with modest increases in risk (10-30%).
- New pathways are implicated by many of these, and these pathways are being investigated.



PGC Cross-Disorder Group, Lancet, 2013

Genetic association in depression

- …Using low-coverage whole-genome sequencing of 5,303 Chinese women with recurrent MDD selected to reduce phenotypic heterogeneity, and 5,337 controls screened to exclude MDD, we identified, and subsequently replicated in an independent sample, two loci contributing to risk of MDD on chromosome 10: one near the SIRT1 gene ($P = 2.53 \times 10(-10)$), the other in an intron of the LHPP gene ($P = 6.45 \times 10(-12)$). Analysis of 4,509 cases with a severe subtype of MDD, melancholia, yielded an increased genetic signal at the SIRT1 locus. We attribute our success to the recruitment of relatively homogeneous cases with severe illness (Cai et al, Nature, 2015).
- The Psychiatric Genomics Consortium now has a paper submitted including 44 loci, based on a sample of >100,000 cases.

Environmental events interacting with genetic liability

- A study by Kendler et al (AJP, 1995) in 2164 female-female twin pairs showed that four types of events were associated with an RR>10:
- Death of a close relative
- Assault
- Serious marital problems
- Divorce/breakup
- Low genetic liability was associated with a risk of 0.5%-6.2% (depending on number of events); high liability with 1.1%-14.6%.

Gene x Environment Interaction (GxE)

- Science, 2003, Caspi A, Moffitt T, and colleagues.
- In 800 subjects from Dunedin, New Zealand, the "short" variant of 5HTTLPR (lower reuptake) predicted depression in the presence of stressful life events in the prior 5 years, but not without such life events.
- This work was widely cited, but has not replicated in large samples.

See Culverhouse et al, Molecular Psychiatry, 2017

Pharmacogenetics of antidepressants

- Pharmacokinetics – P450 system enzymes are important, esp. CYP2D6.
- PM, IM, EM, and UM groups were classified for TCAs. These distinctions are less relevant for SSRIs and SNRIs (less clear connection between blood level and response).
- Pharmacodynamics – L allele of 5HTTLPR assoc w better response to SSRI – needs replication.
- HTR2A is a candidate for response.
- Many candidates for Treatment Emergent Suicidal Ideation, including glutamate receptor genes.

Lohoff et al, 2012

International collaboration confirms specific genetic locations for bipolar disorder

Psychiatric GWAS Consortium Bipolar Disorder Working Group Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near *ODZ4*

***Nature Genetics* 43, 977–983 (2011) doi:10.1038/ng.943**

We conducted a combined genome-wide association study (GWAS) of 7,481 individuals with bipolar disorder (cases) and 9,250 controls as part of the Psychiatric GWAS Consortium.…**An analysis of all 11,974 bipolar disorder cases and 51,792 controls confirmed genome-wide significant evidence of association for *CACNA1C* and identified a new intronic variant in *ODZ4.* We identified a pathway comprised of subunits of calcium channels enriched in bipolar disorder association intervals.** Finally, a combined GWAS analysis of schizophrenia and bipolar disorder yielded strong association evidence for SNPs in *CACNA1C* and in the region of *NEK4-ITIH1-ITIH3-ITIH4*. Our replication results imply that increasing sample sizes in bipolar disorder will confirm many additional loci.

Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis

Cross-Disorder Group of the Psychiatric Genomics Consortium

Methods: We analysed genome-wide single-nucleotide polymorphism (SNP) data for the five disorders in 33 332 cases and 27 888 controls of European ancestry. To characterise allelic effects on each disorder, we applied a multinomial logistic regression procedure with model selection to identify the best-fitting model of relations between genotype and phenotype.

Findings: SNPs at four loci surpassed the cutoff for genome-wide significance ($p<5\times10^{-8}$) in the primary analysis: regions on chromosomes 3p21 and 10q24, and SNPs within two L-type voltage-gated calcium channel subunits, *CACNA1C* and *CACNB2*. Model selection analysis supported effects of these loci for several disorders. ….Polygenic risk scores showed cross-disorder associations, notably between adult-onset disorders. Pathway analysis supported a role for calcium channel signalling genes for all five disorders. Finally, SNPs with evidence of cross-disorder association were enriched for brain eQTL markers.

Interpretation: Our findings show that specific SNPs are associated with a range of psychiatric disorders of childhood onset or adult onset. In particular, variation in calcium-channel activity genes seems to have pleiotropic effects on psychopathology.

Funding National Institute of Mental Health.

www.thelancet.com **Published online February 28, 2013**
http://dx.doi.org/10.1016/S0140-6736(12)62129-1

Genetic relationships of major psychiatric disorders

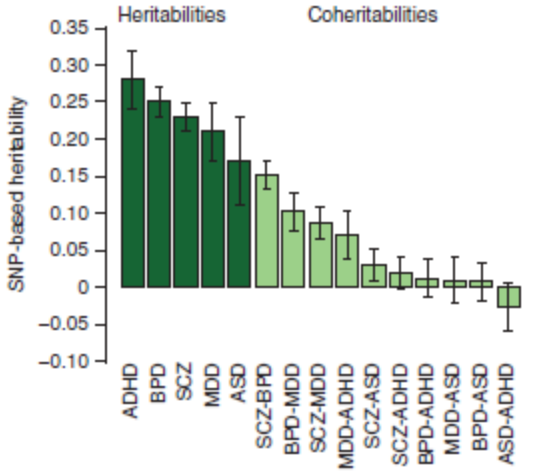


Figure 1 Evidence for genome-wide pleiotropy between psychiatric disorders. Proportion of variance in liability (SNP-based heritability) and proportion of covariance in liability between disorder (SNP-based coheritability) for five major psychiatric disorders. The 95% error bars represent the estimates ± 1.96 s.e. SCZ, schizophrenia; MDD, major depressive disorder; BPD, bipolar disorder.

Cross-Disorder Group of the Psychiatric Genomics Consortium, Nature Genetics, 2013

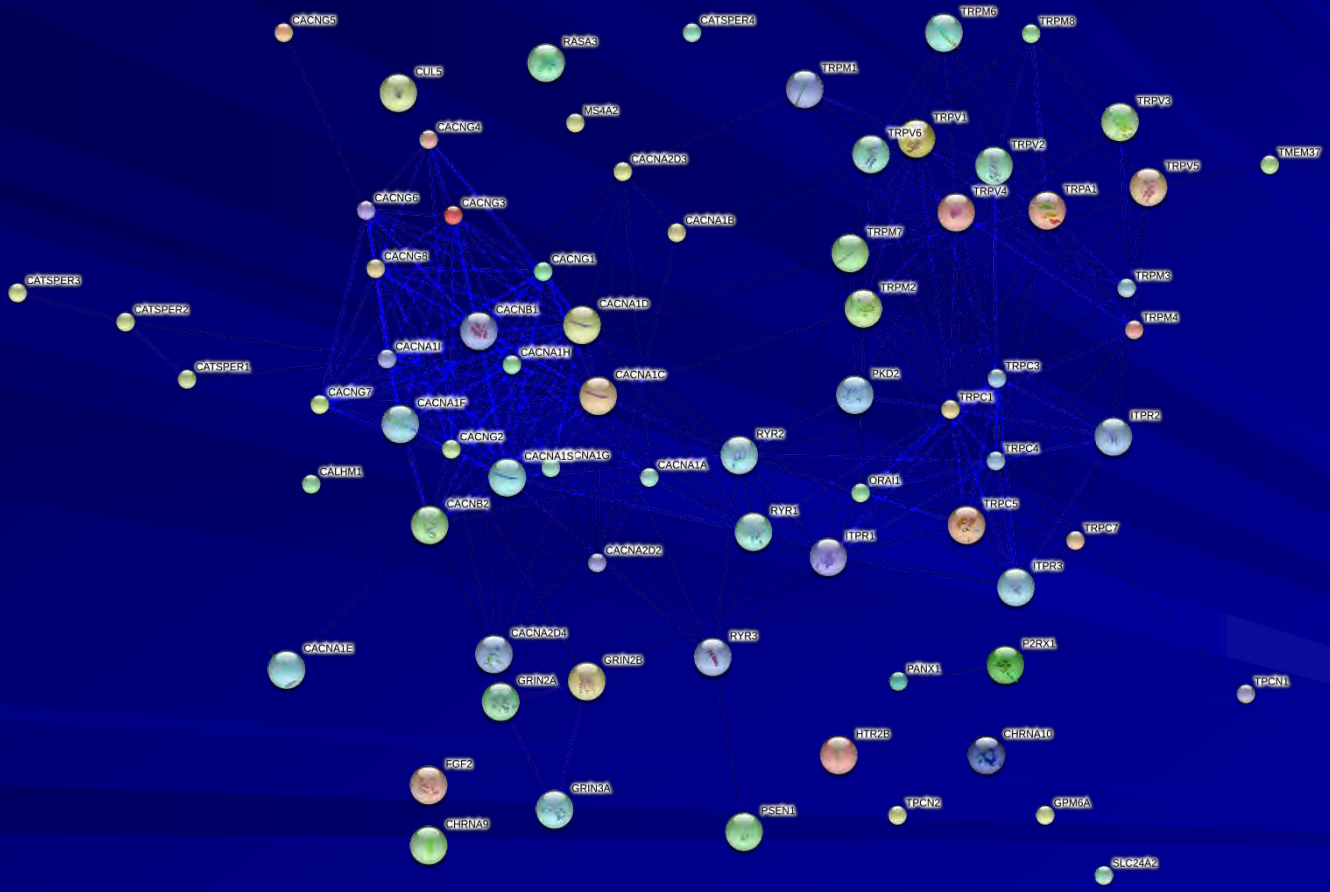
New Methods in Genetic Studies

- Genome-wide association studies – 1M or more markers
- Copy number variation (CNVs)– clearly important in SZ and autism
- Studies of gene methylation and regulation.
- Next generation sequencing/whole genome sequencing.
- Skin or blood cells can provide stem cells; these can be induced to grow into neuronal cells.

CACNA1C (Chr 12p13.33)

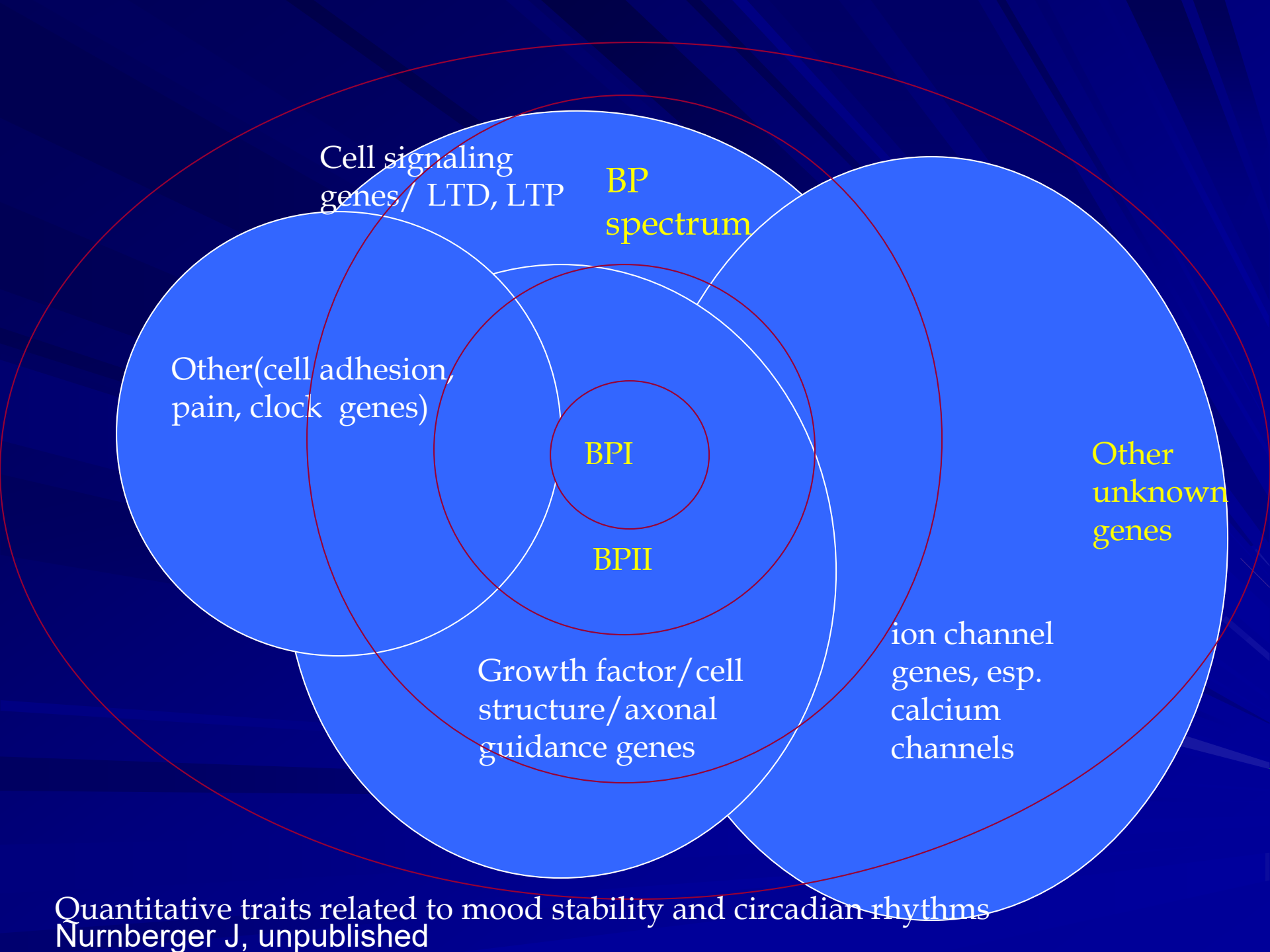
- Codes for the alpha1C subunit of the L type voltage dependent Calcium channel.
- The gene spans 150 kb and includes 44-50 exons.
- The alpha 1 subunit consists of 24 transmembrane segments, divided into four groups around a central pore.
- S4 segments are membrane-spanning, and may constitute the voltage sensor (Alsobrook and Stevens, 1988).

Functional relationship between calcium channel activity genes defined by Gene Ontology



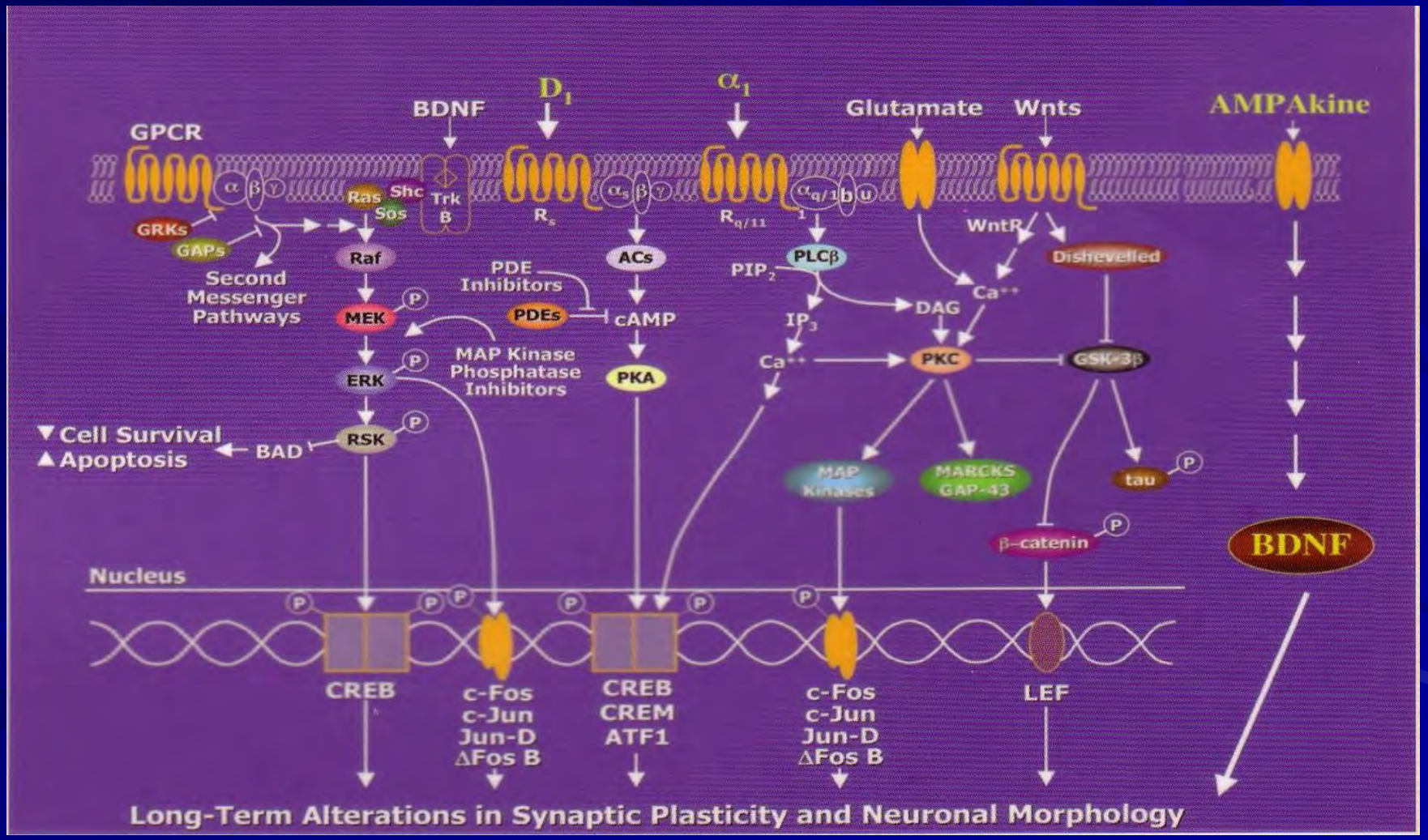
XXIII.$Figure$12. Functional$relationships$between73calcium$channel$activity$genes$definedbyGene$Ontology$(http://amigo.geneontology.org/cgi-bin/amigo/term_details?term=GO:0005262). The network view

PGC Cross-Disorder Group, Lancet, 2013



Quantitative traits related to mood stability and circadian rhythms
Nurnberger J, unpublished

Intracellular Signaling Pathways Involved in Neural Plasticity



Gould, 2004, Molecular Psychiatry.

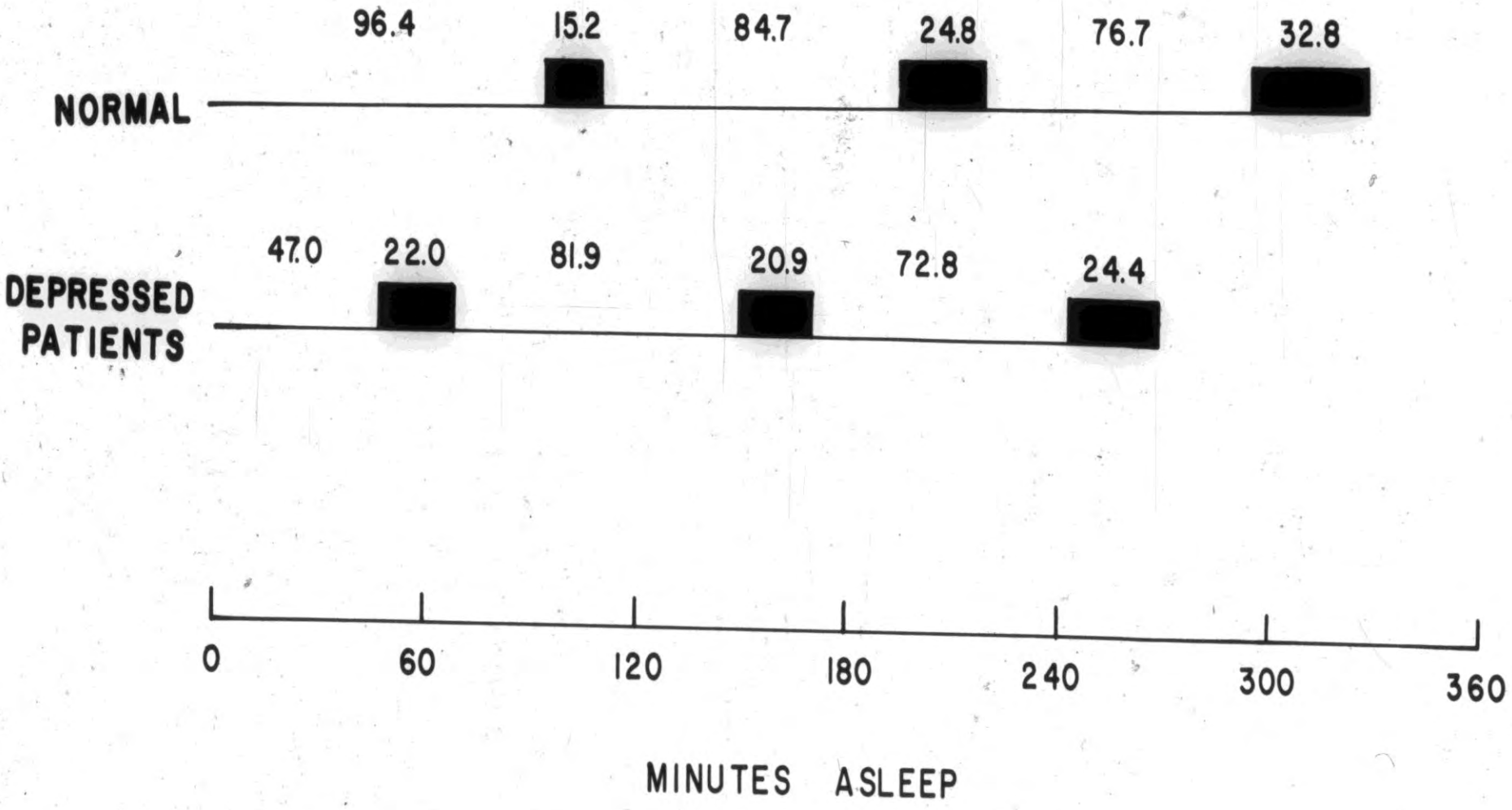
Dopaminergic Stimulation May Cause a Manic Syndrome

- Amphetamine and cocaine may produce a substance-induced mania.
- The use of dopaminergic agonist medications such as L-DOPA and bromocryptine is also associated with mania.
- These effects may be blocked or treated with dopamine antagonists such as the neuroleptics.

Cholinergic Stimulation May Cause a Depressive Syndrome

- Physostigmine (but not neostigmine)
- Arecoline
- Organophosphate toxins
- Oxotremorine
- Precursors - lecithin, deanol, choline
- May decrease manic symptoms
- May be reversed with atropine

COMPARISON OF DEPRESSED SLEEP PATTERNS WITH NORMALS



Serotonin Dysregulation in Mood Disorder

- Low 5HIAA in the spinal fluid is associated with impulsivity and aggression.
- Tryptophan depletion results in depressive relapse.
- Decreased cortisol and prolactin response to tryptophan.
- Decreased 5HT uptake in platelets from depressed patients.
- “Short” form of serotonin transporter gene associated with risk for depression.

Hypothalamic-Pituitary-Adrenal Axis abnormalities in mood disorder

- Increased secretion of cortisol over the 24-hour day.
- Decreased suppression of cortisol by dexamethasone in about 50% of patients with major depression.
- Increased corticotropin releasing hormone in spinal fluid.
- Blunted ACTH response to CRF.
- Adrenal gland hypertrophy in some patients.

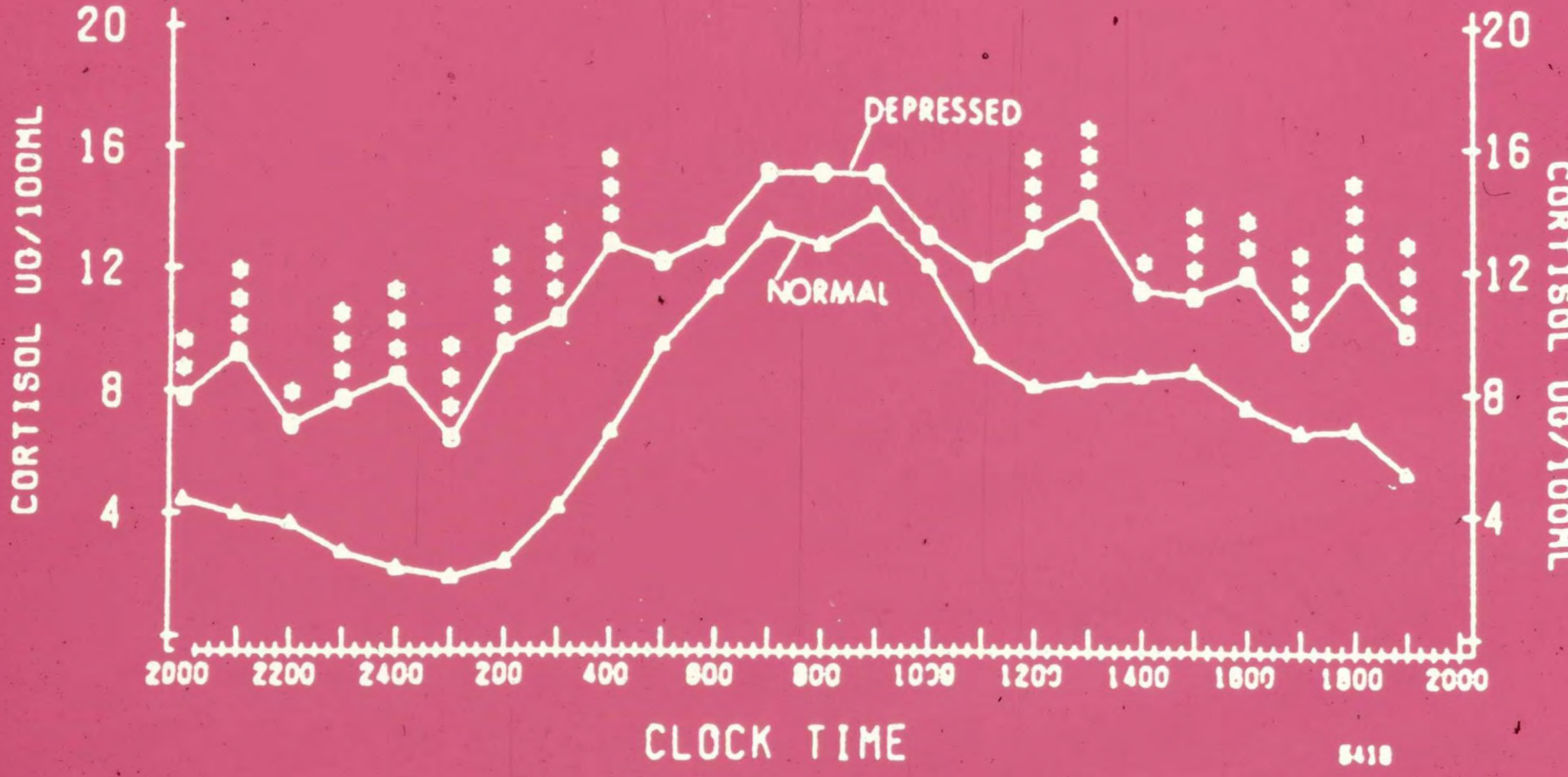


FIGURE 2. Mean hourly cortisol concentration of 7 depressed and 54 normal individuals. * = $p < .05$; ** = $p < .01$; and *** = $p < .001$.

Sachar, 1977

Noradrenergic Dysregulation in Depression

- Blunted growth hormone response to clonidine suggests decreased alpha2 receptor sensitivity.
- Metabolite studies show high variability in affective patient groups. Uniform increases or decreases are not found.

Neurobiological Effects of Antidepressant Treatment

- Most antidepressants increase monoamine activity acutely.
- Decrease in norepinephrine receptor activity (and cyclic AMP activity) is seen after several weeks.
- Upregulation of cyclic AMP response element binding protein (CREB) and brain derived neurotrophic factor (BDNF) is also seen.
- New neuronal growth (neurogenesis) in the hippocampus may be necessary for recovery from depression.

GABA Dysfunction in Affective Disorders

- Low plasma GABA has been found in depression in many studies (Petty).
- GABA dysfunction is seen in autopsy brain samples from subjects with bipolar illness in limbic areas, including the hippocampus and the anterior cingulate cortex (Benes).
- CSF GABA fluctuates with mood state (Berrettini).

Anatomic Localization of Affective Symptomatology

- Patients with stroke or traumatic brain injury are more likely to show depression if the lesion is in the frontal lobe (esp. left?)
- Mania appears to be related to lesions of the right basotemporal cortex.
- Metabolism in the dorsal prefrontal cortex is generally decreased in depression (related to cognition).
- Metabolism in the orbital cortex is increased (related to perseveration).
- The amygdala also shows increased activation in depression; this may be related to emotional behavior. The *limbic circuit* also involves the anterior cingulate cortex and the hippocampus.

Outcome in Bipolar Illness

- Bipolar patients may show substantial variation in outcome.
- The traditional expectation was for restoration of normal functioning between episodes.
- However, in clinical practice, some patients show functional deterioration over time.
- In our experience, ~20% of patients describe themselves as “disabled”.
- There is some evidence for increased risk for dementia with multiple episodes of depression and mania (Kessing and Anderson, 2004).

Conclusions

- Bipolar disorder is highly heritable (~80%). Major depression somewhat less so (~50%) but still substantially heritable.
- Single genes related to bipolar disorder are now being identified and replicated. There appear to be many genes involved, each having a small effect on risk.
- The best evidence currently is for genes involved in ion channels, neuronal growth and cell signaling.

Conclusions 2

- Bipolar disorder appears to share some aspects of genetic vulnerability with other disorders including schizophrenia, major depression, and childhood disorders such as ADHD and autism.
- Co-occurring disorders (such as substance abuse and anxiety disorders) also appear to be important in the inheritance of vulnerability to bipolar disorder.
- Specific genes implicated suggest that calcium channel abnormalities are involved in several of these disorders. This may have implications for development of new treatment strategies.