A manic depressive history:
The genetic dissection of complex neuropsychiatric disorders

Sven Cichon, PhD

Professor of Medical Genetics

Medical Genetics I University Hospital Basel
Department of Biomedicine I University of Basel

Universitätsspital Basel

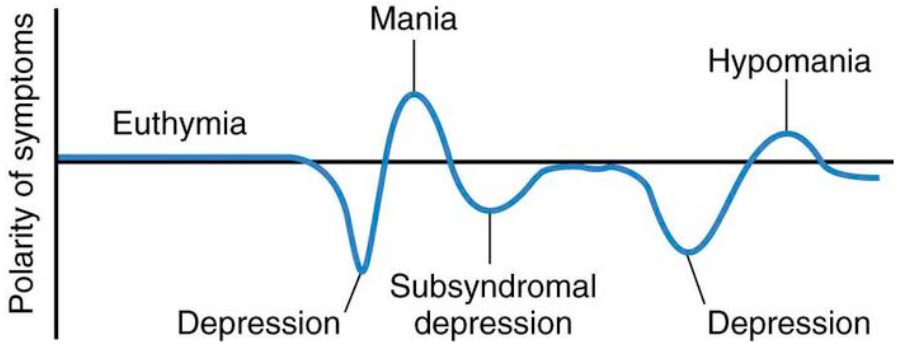
HBP workshop
Innsbruck, 06.07.2017

Departement Biomedizin Basel

Bipolar disorder (BD)

- Complex disorder of mood characterized by recurrent episodes of mania and depression
- Lifetime prevalence of about 1%
- High heritability of about 60-80%

en.wikipedia.org



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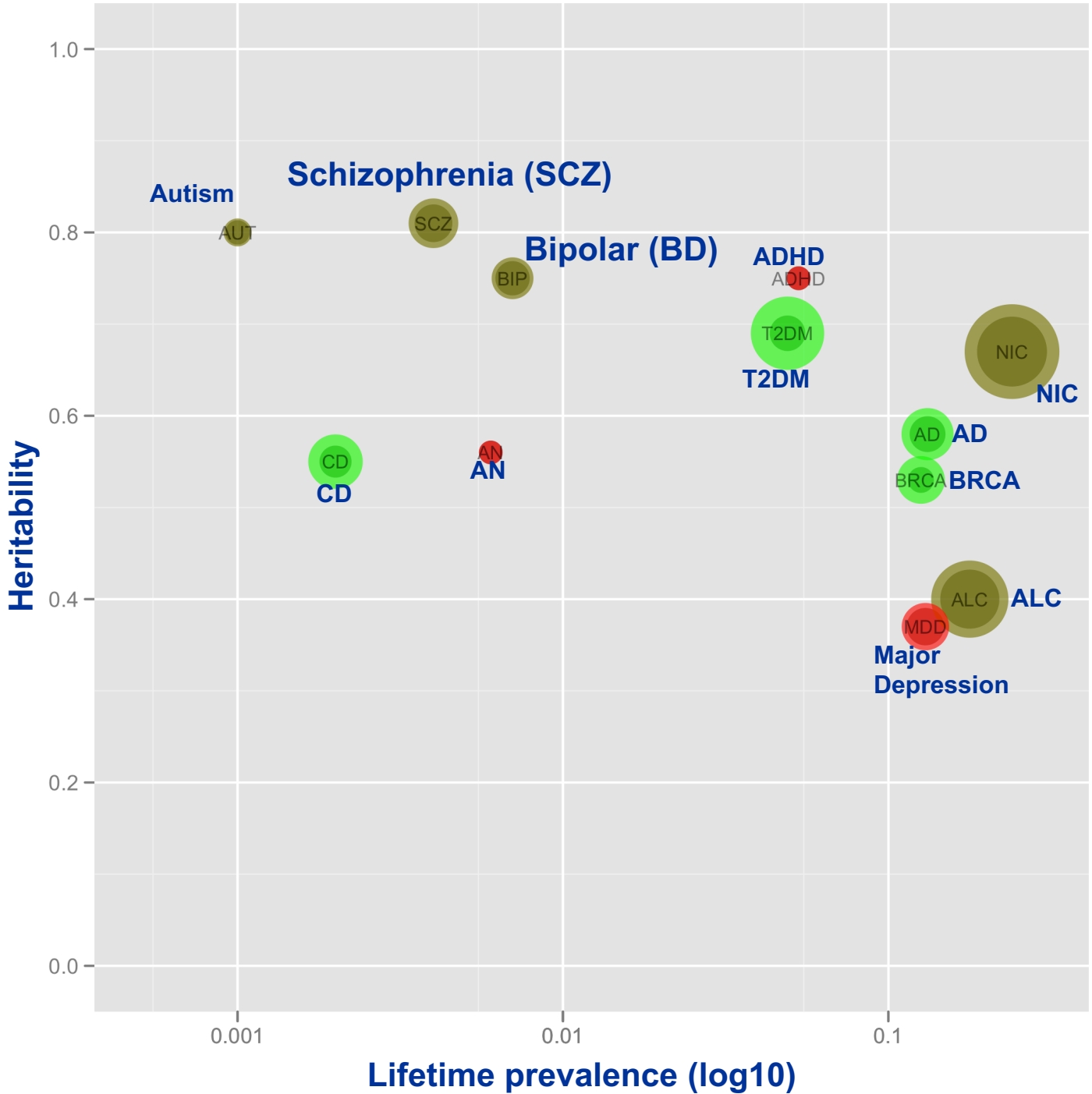


Sullivan et al., 2012

Aims of molecular genetic research in psychiatry

Identification of disease genes

understanding

Pathophysiology

Pharmacology

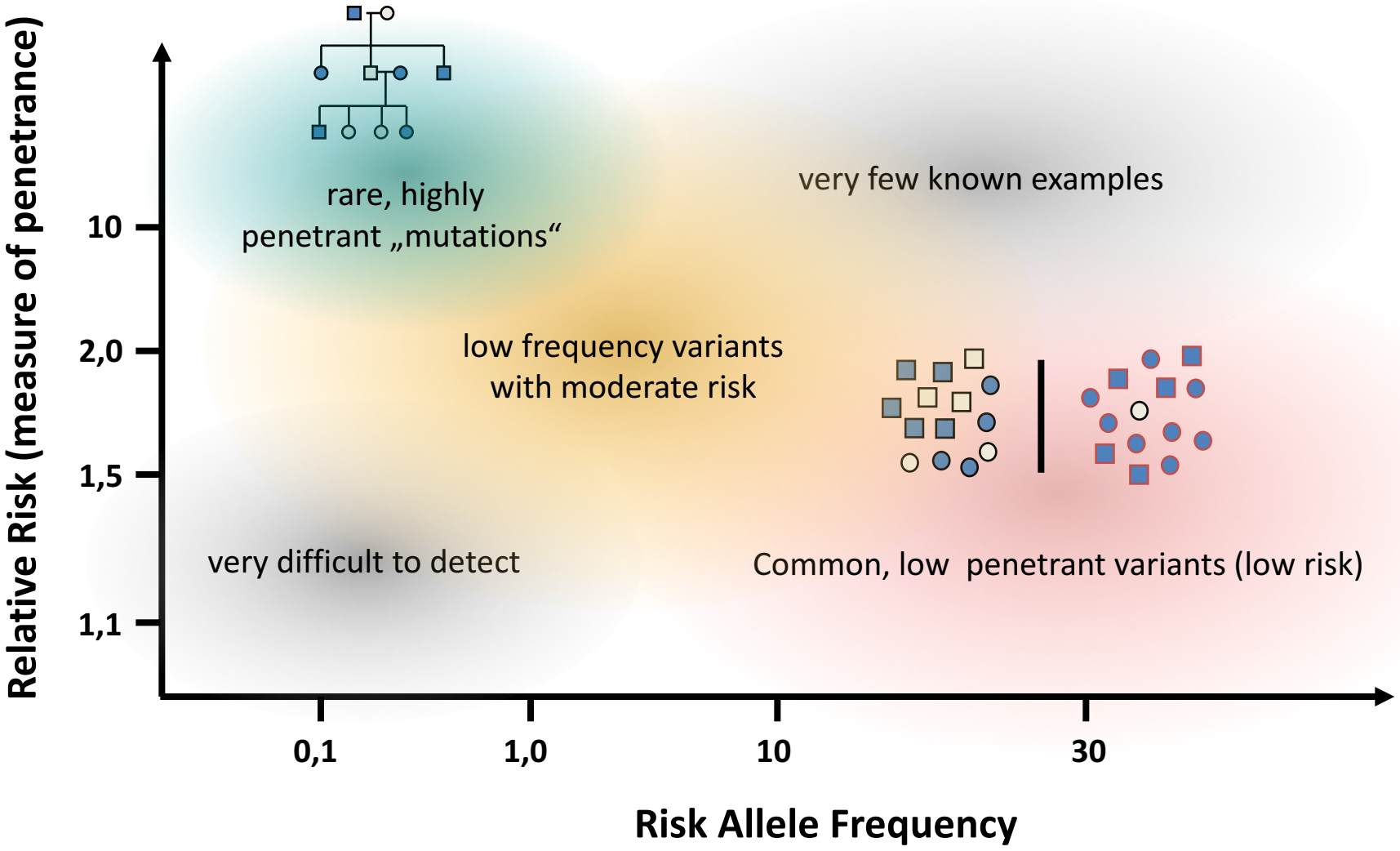
Epidemiology

Evolutionary aspects

application

- Classification of disease
- Development of new therapeutics
- Individually tailored medication (precision medicine)
- Specific prevention based on early diagnosis

Strategies to identify genetic risk factors in complex diseases



Research follows genomics knowledge and available technology

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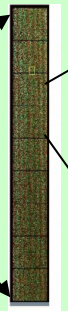
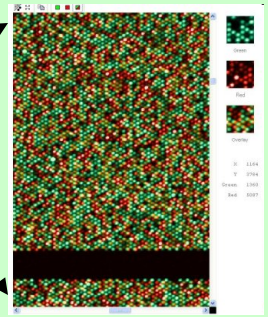
Sequencing





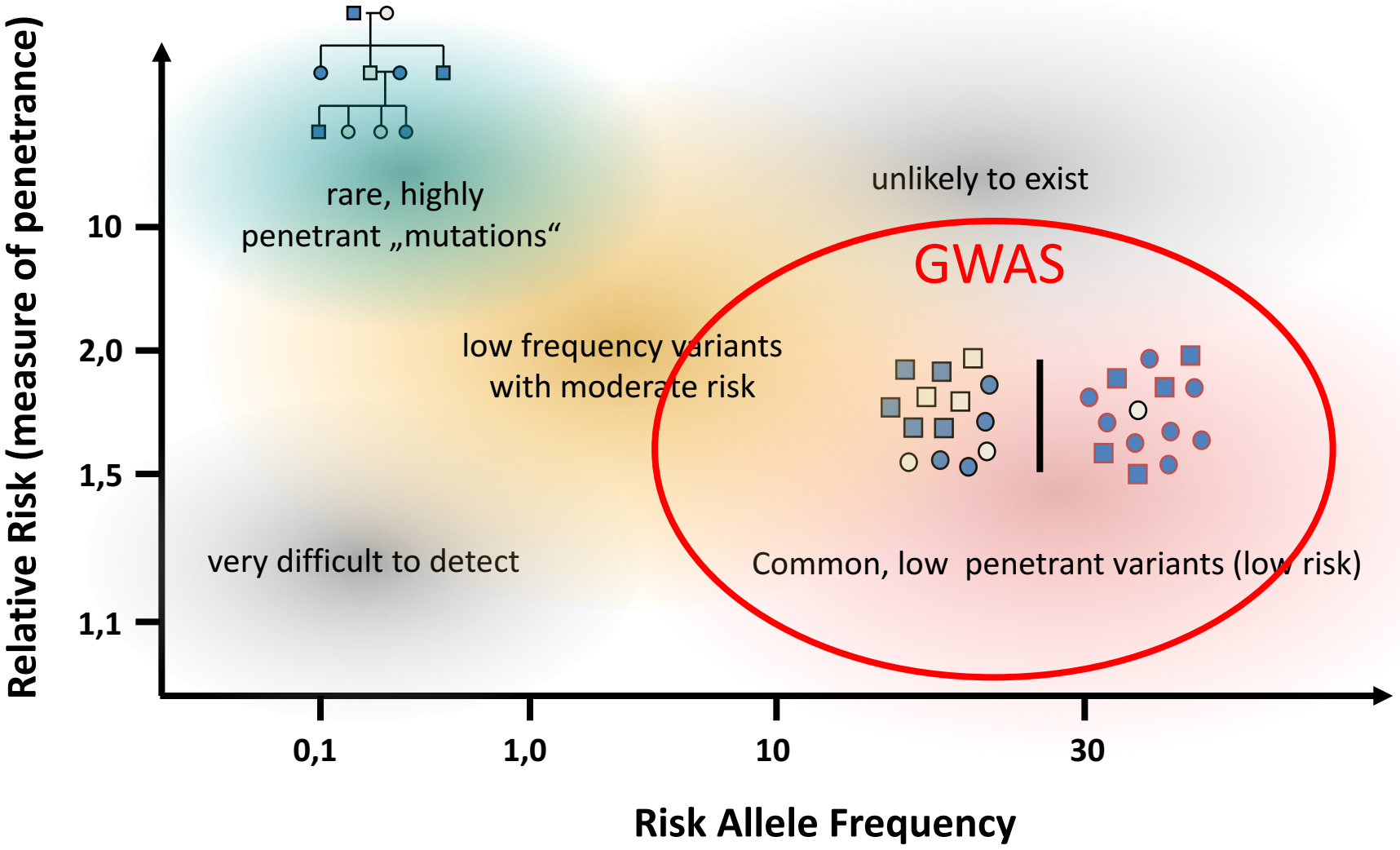
CNVs

GWAS

Linkage / candidate gene studies

1990 | 1995 | 2000 | 2005 | 2010 | 2015

Strategies to identify genetic risk factors in complex diseases



First GWAS in bipolar disorder

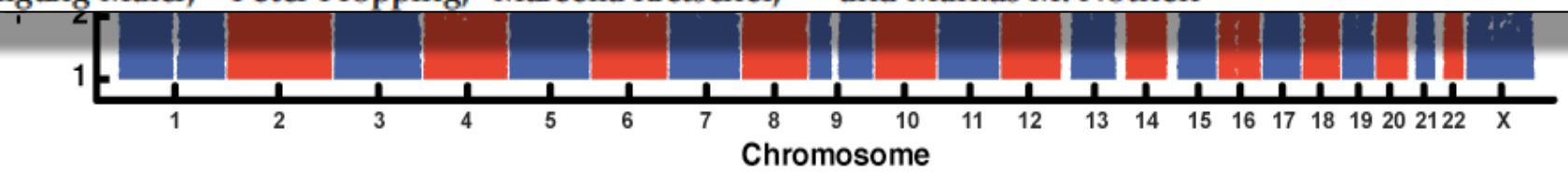
Departement Biomedizin Basel

Universitätsspital Basel

REPORT

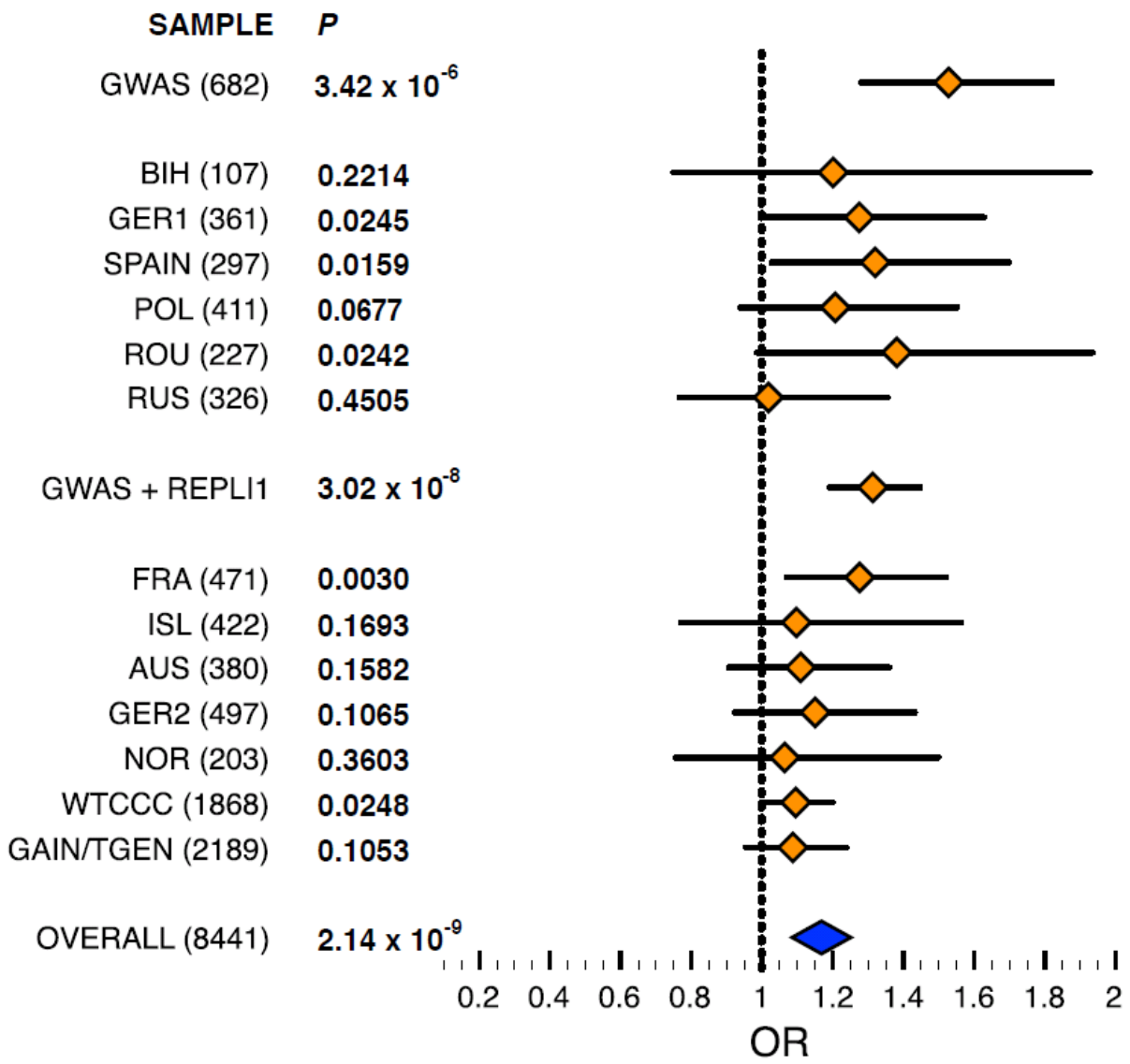
Genome-wide Association Study Identifies Genetic Variation in Neurocan as a Susceptibility Factor for Bipolar Disorder

Sven Cichon,[1,2,3,44,*] Thomas W. Mühleisen,[2,3,44] Franziska A. Degenhardt,[2,3] Manuel Mattheisen,[2,3,4] Xavier Miró,[5] Jana Strohmaier,[6] Michael Steffens,[4] Christian Meesters,[4] Stefan Herms,[2,3] Moritz Weingarten,[2,3] Lutz Priebe,[2,3] Britta Haenisch,[2,3] Michael Alexander,[2,3] Jennifer Vollmer,[2,3] René Breuer,[6] Christine Schmäl,[6] Peter Tessmann,[2,3] Susanne Moebus,[7] H.-Erich Wichmann,[8,9,10] Stefan Schreiber,[11] Bertram Müller-Myhsok,[12] Susanne Lucae,[12] Stéphane Jamain,[13,14,15] Marion Leboyer,[13,14,15] Frank Bellivier,[13,14,15] Bruno Etain,[13,14,15] Chantal Henry,[13,14,15] Jean-Pierre Kahn,[16] Simon Heath,[17] Bipolar Disorder Genome Study (BiGS) Consortium,[18] Marian Hamshere,[19] Michael C. O'Donovan,[19] Michael J. Owen,[19] Nick Craddock,[19] Markus Schwarz,[20] Helmut Vedder,[20] Jutta Kammerer-Ciernioch,[20] Andreas Reif,[21] Johanna Sasse,[22] Michael Bauer,[22] Martin Hautzinger,[23] Adam Wright,[24,25] Philip B. Mitchell,[24,25] Peter R. Schofield,[26,27] Grant W. Montgomery,[28] Sarah E. Medland,[28] Scott D. Gordon,[28] Nicholas G. Martin,[28] Omar Gustafsson,[29] Ole Andreassen,[29,30] Srdjan Djurovic,[29,30,31] Engilbert Sigurdsson,[32] Stacy Steinberg,[33] Hreinn Stefansson,[33] Kari Stefansson,[33,34] Lejla Kapur-Pojskic,[35] Liliana Oruc,[36] Fabio Rivas,[37] Fermín Mayoral,[37] Alexander Chuchalin,[38] Gulja Babadjanova,[38] Alexander S. Tiganov,[39] Galina Pantelejeva,[39] Lilia I. Abramova,[39] Maria Grigoroiu-Serbanescu,[40] Carmen C. Diaconu,[41] Piotr M. Czerski,[42] Joanna Hauser,[42] Andreas Zimmer,[5] Mark Lathrop,[17] Thomas G. Schulze,[43] Thomas F. Wienker,[4] Johannes Schumacher,[3] Wolfgang Maier,[44] Peter Propping,[3] Marcella Rietschel,[6,45] and Markus M. Nöthen[2,3,45]



Cichon, Mühleisen et al., AJHG (2011)

Neurocan (NCAN) rs 1064395
in 8,400 bipolar patients / 35,300 controls

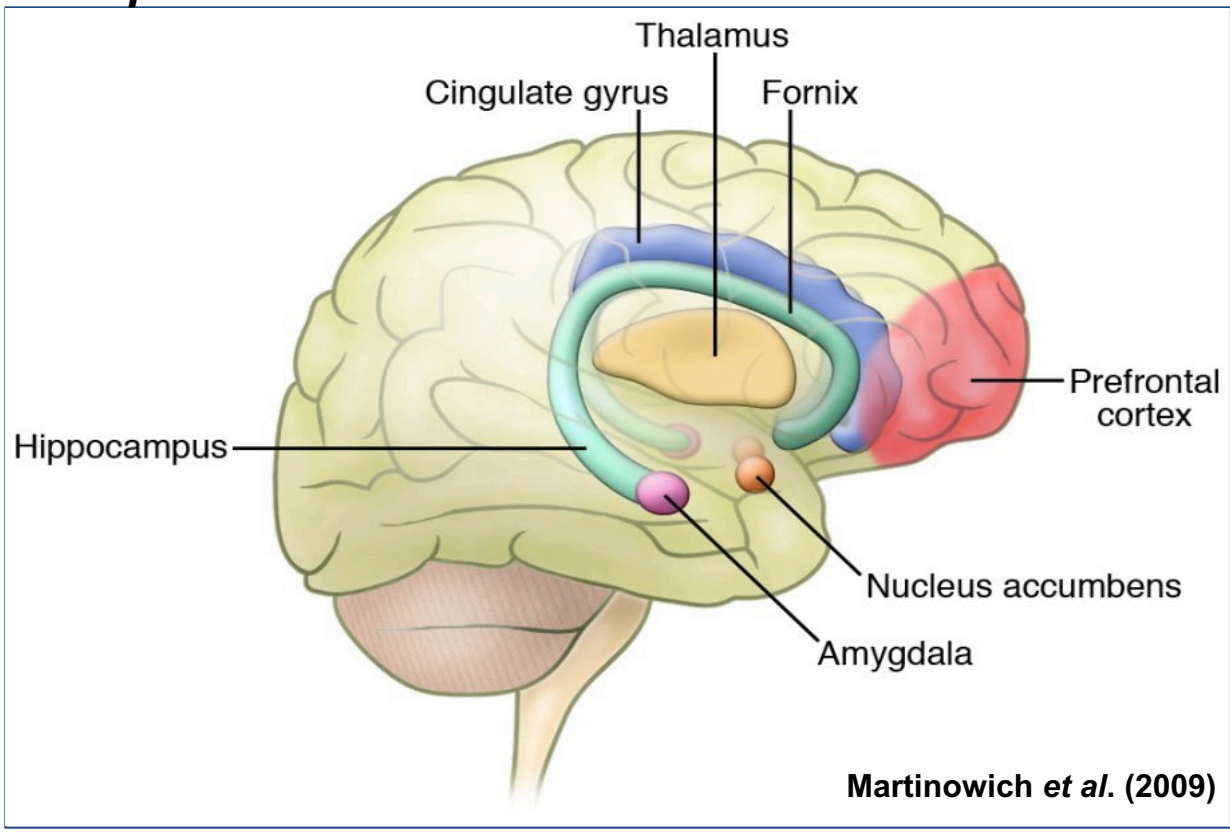


Cichon, Mühleisen et al., AJHG (2011)

Neurocan (NCAN) is a proteoglycan involved in neurodevelopment

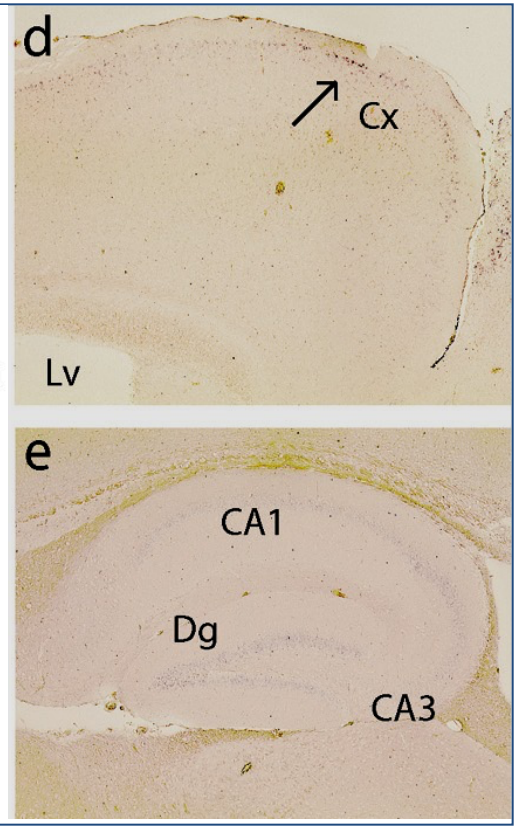
- **Extracellular matrix proteoglycan**
- **Cell adhesion and migration**

H. sapiens



Martinowich *et al*. (2009)

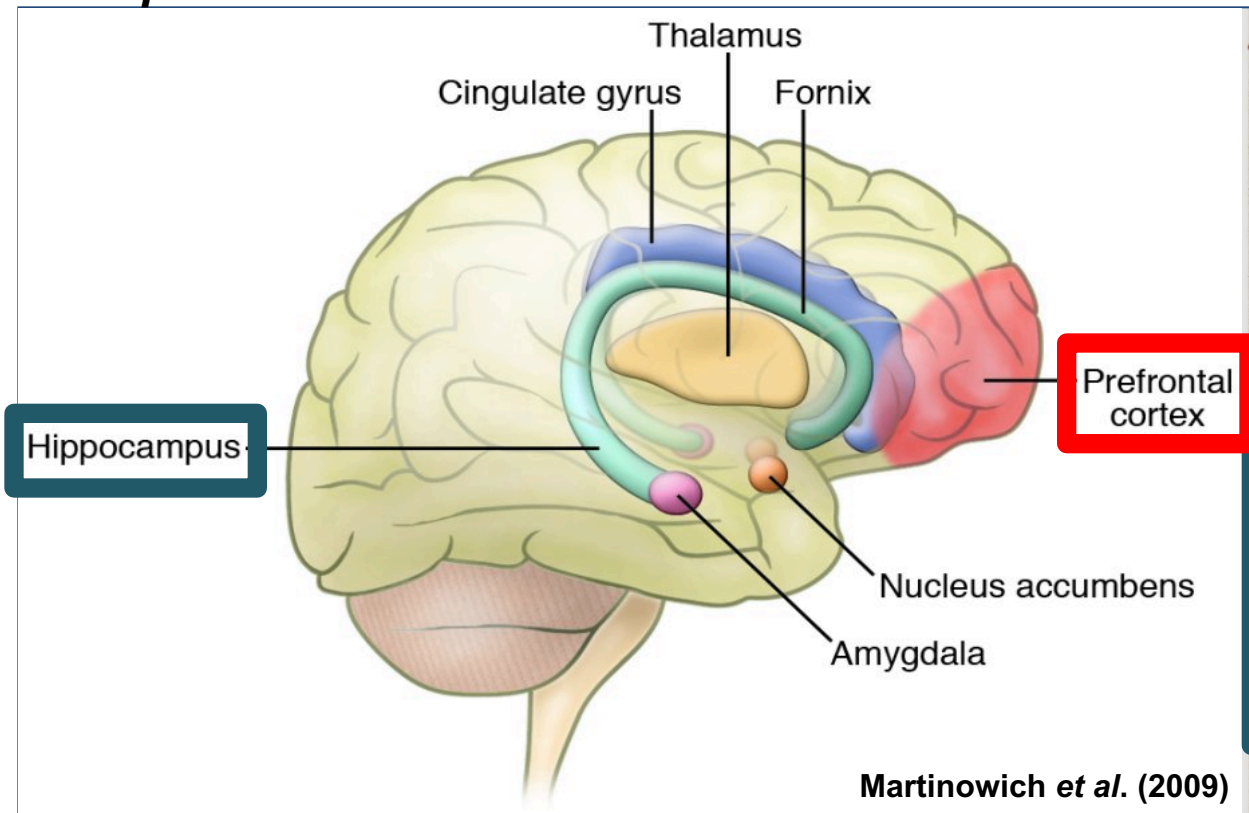
M. musculus



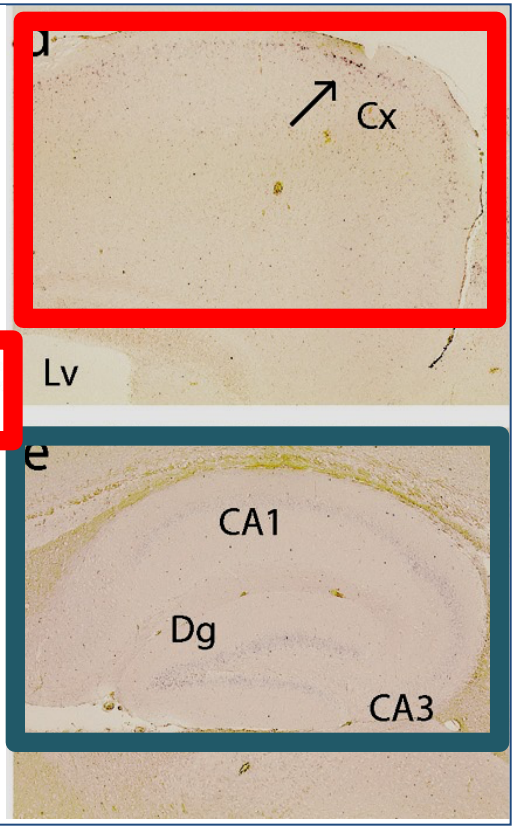
Neurocan (NCAN) is a proteoglycan involved in neurodevelopment

- **Highly expressed in cortex and hippocampus**
- **Areas related to BD by neuroimaging studies**

H. sapiens



M. musculus



Martinowich *et al*. (2009)

Second GWAS in bipolar disorder

nature COMMUNICATIONS

ARTICLE

Received 14 Aug 2013 | Accepted 29 Jan 2014 | Published 11 Mar 2014

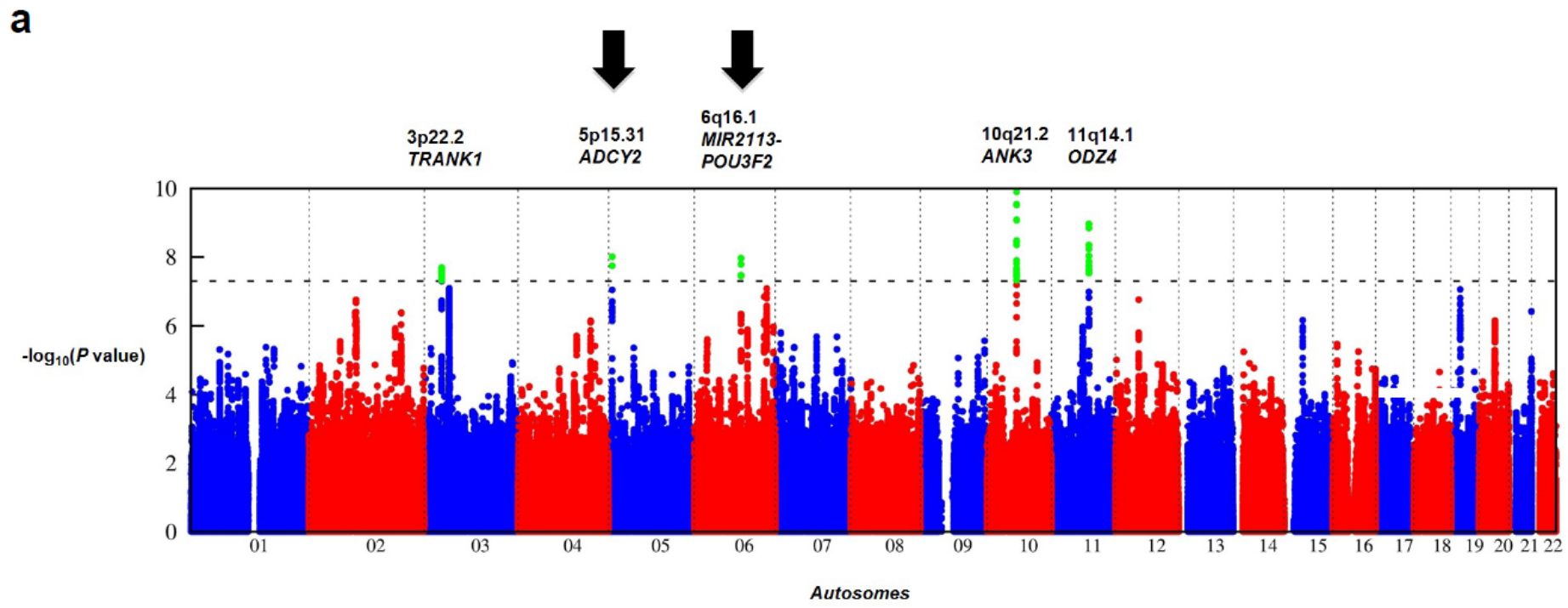
DOI: 10.1038/ncomms4339

Genome-wide association study reveals two new risk loci for bipolar disorder

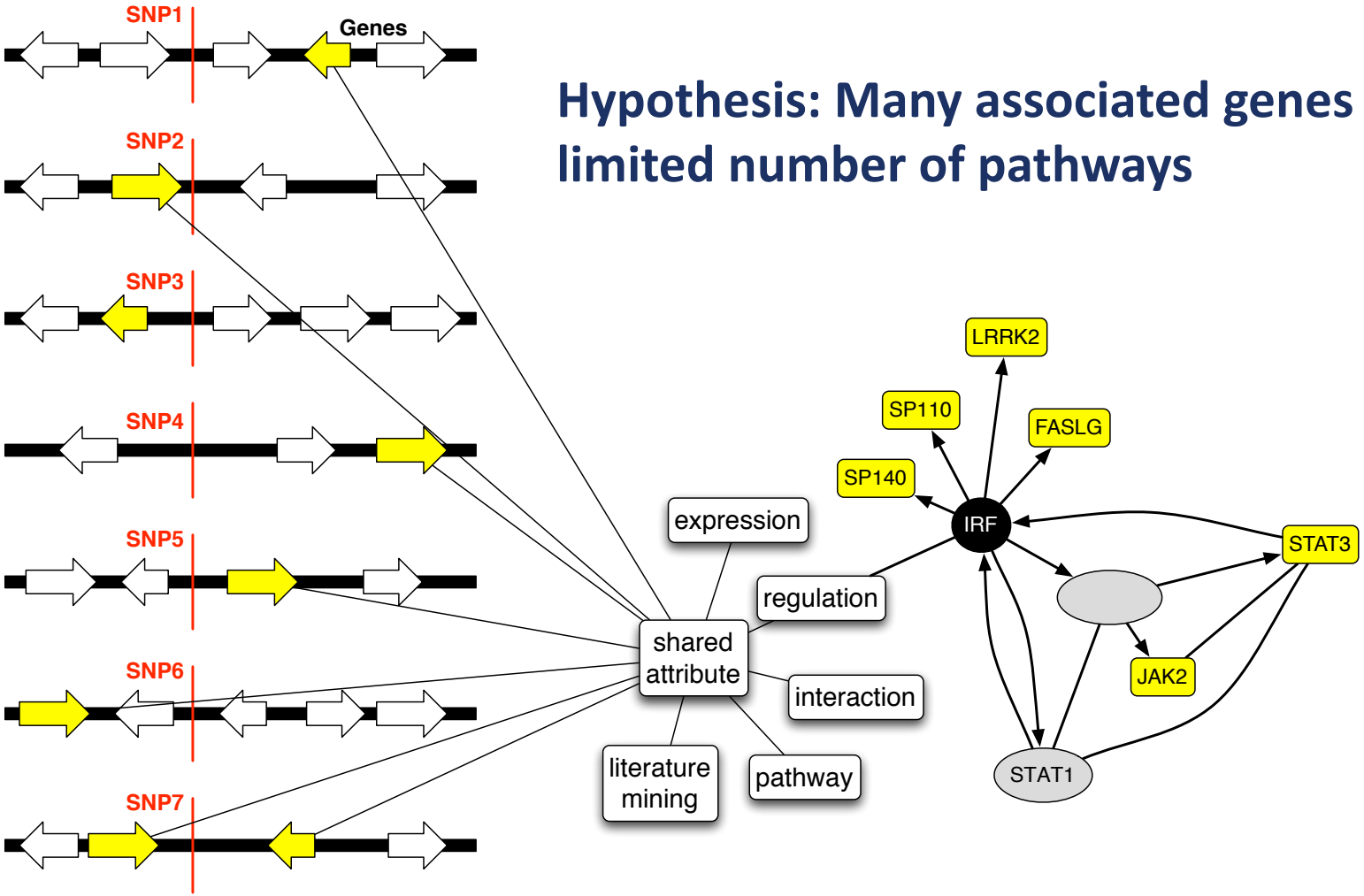
Thomas W. Mühleisen[1,2,3,*], Markus Leber[4,5,*], Thomas G. Schulze[6,*], Jana Strohmaier[7], Franziska Degenhardt[1,2], Jens Treutlein[7], Manuel Mattheisen[8,9], Andreas J. Forstner[1,2], Johannes Schumacher[1,2], René Breuer[7], Sandra Meier[7,10], Stefan Herms[1,2,11], Per Hoffmann[1,2,3,11], André Lacour[5], Stephanie H. Witt[7], Andreas Reif[12], Bertram Müller-Myhsok[13,14,15], Susanne Lucae[13], Wolfgang Maier[16], Markus Schwarz[17], Helmut Vedder[17], Jutta Kammerer-Ciernioch[17], Andrea Pfennig[18], Michael Bauer[18], Martin Hautzinger[19], Susanne Moebus[20], Lutz Priebe[1,2], Piotr M. Czerski[21], Joanna Hauser[21], Jolanta Lissowska[22], Neonila Szeszenia-Dabrowska[23], Paul Brennan[24], James D. McKay[25], Adam Wright[26,27], Philip B. Mitchell[26,27], Janice M. Fullerton[28,29], Peter R. Schofield[28,29], Grant W. Montgomery[30], Sarah E. Medland[30], Scott D. Gordon[30], Nicholas G. Martin[30], Valery Krasnow[31], Alexander Chuchalin[32], Gulja Babadjanova[32], Galina Pantelejeva[33], Lilia I. Abramova[33], Alexander S. Tiganov[33], Alexey Polonikov[34], Elza Khusnutdinova[35], Martin Alda[36,37], Paul Grof[37,38,39], Guy A. Rouleau[40], Gustavo Turecki[41], Catherine Laprise[42], Fabio Rivas[43], Fermin Mayoral[43], Manolis Kogevinas[44], Maria Grigoroiu-Serbanescu[45], Peter Propping[1], Tim Becker[5,4], Marcella Rietschel[7,*], Markus M. Nöthen[1,2,*] & Sven Cichon[1,2,3,11,*]

Second GWAS in bipolar disorder

- Largest existing GWAS dataset of bipolar disorder
  (Mühleisen et al., Nature Communications, 2014)
- 9,747 patients and 14,278 controls, obtained from four European countries, Canada, and Australia plus multinational Psychiatric Genomics Consortium (Sklar et al., 2011)
- Five genome-wide significant loci:
  - Three previously identified loci (*ANK3*, *ODZ4* and *TRANK1*)
  - *ADCY2* and *MIR2113 -POU3F2*



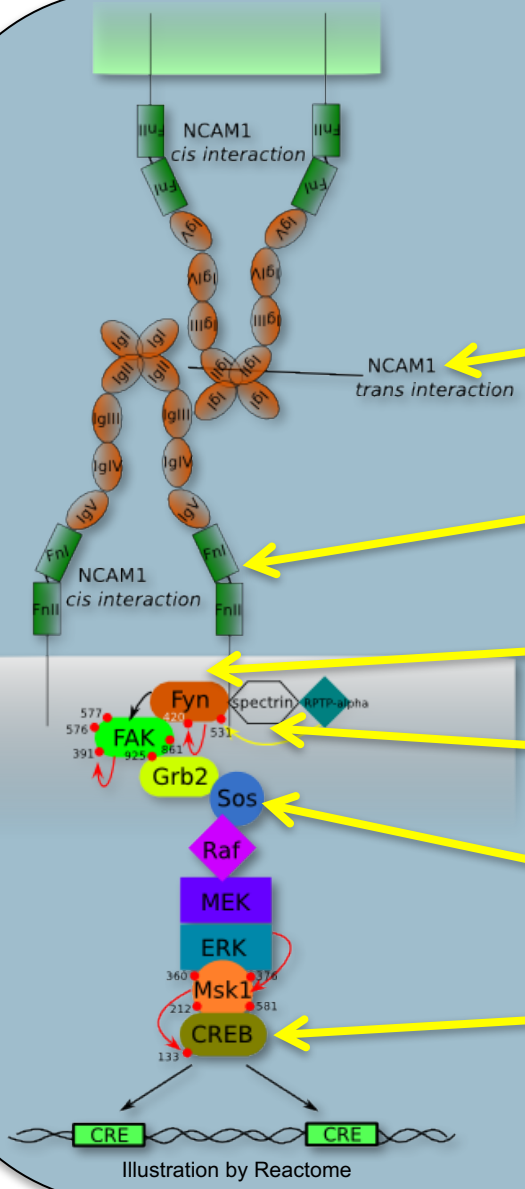
GWAS as starting point for pathway analyses



Hypothesis: Many associated genes implicate limited number of pathways

Proof: Statistically significant excess connectivity of genes in GWAS regions

Genes Enriched in NCAM Signaling – Pathway Hierarchy



- **Neural cell adhesion molecule** pathway plays a crucial role in neuronal development, synaptic plasticity, and regeneration
- Outgrowth of axons and dendrites is the most studied **NCAM** function
- Pathway-based enrichment analysis in BD provided evidence for:

Extracellular **neurocan** (***NCAN***) interferes with NCAM1 and inhibits neuronal adhesion and neurite outgrowth

NCAM1 clusters with **voltage-dependent calcium channels (*CACNA1C*, *CACNA1D*, *CACNB2*, *CACNB3*)** in growth cones leading to Ca2+ influx that promotes neurotransmitter release

tyrosine kinases *FYN* and *FAK*

β-Spectrins (*SPTBN1*, *SPTBN2*)

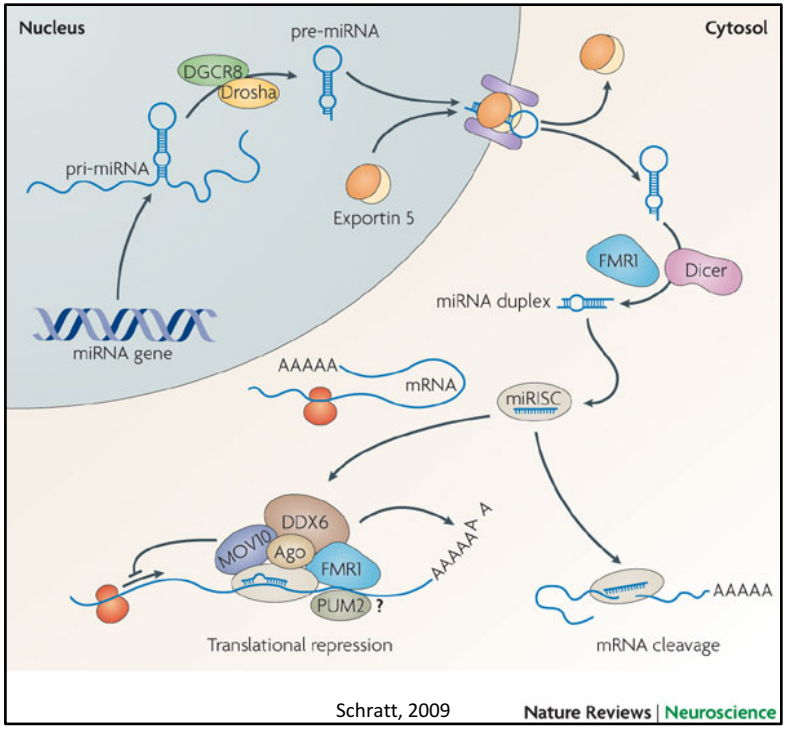
Upon formation of the FAK-GRB2-SOS complex, SOS activates the **GTPase *KRAS***

cAMP response element-binding protein (*CREB1*) activates expression of genes for axonal growth, survival, synaptic plasticity

Mühleisen, Reinbold *et al.*, J. of Affective Disorders, in press

Candidate-gene-class-driven analysis of the GWAS data: influence of microRNAs on development of BD

- Small non-coding RNAs
- Control of the expression of target genes
- Contribution to the basic mechanisms underlying brain development and plasticity (Fineberg et al., 2009; Schratt, 2009)
- Possible involvement in the pathogenesis of psychiatric disorders (Xu et al., 2010; Forstner et al., 2013), including bipolar disorder (Moreau et al., 2011)



Genome-wide analysis of microRNA coding genes

OPEN

Citation: Transl Psychiatry (2015) **5**, e678; doi:10.1038/tp.2015.159

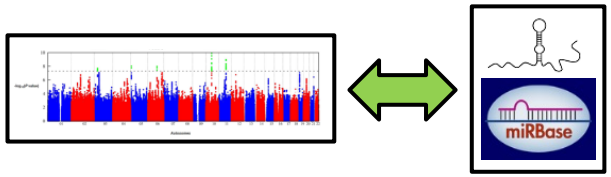
www.nature.com/tp

ORIGINAL ARTICLE

Genome-wide analysis implicates microRNAs and their target genes in the development of bipolar disorder

AJ Forstner[1,2,50], A Hofmann[1,2,50], A Maaser[1,2], S Sumer[3], S Khudayberdiev[3], TW Mühleisen[1,2,4], M Leber[5], TG Schulze[6], J Strohmaier[7], F Degenhardt[1,2], J Treutlein[7], M Mattheisen[8,9], J Schumacher[1,2], R Breuer[7], S Meier[7,10], S Herms[1,2,11], P Hoffmann[1,2,4,11], A Lacour[12], SH Witt[7], A Reif[13], B Müller-Myhsok[14,15,16], S Lucae[14], W Maier[17], M Schwarz[18], H Vedder[18], J Kammerer-Ciernioch[19], A Pfennig[20], M Bauer[20], M Hautzinger[21], S Moebus[22], L Priebe[1,2], S Sivalingam[1,2], A Verhaert[1,2], H Schulz[23], PM Czerski[24], J Hauser[24], J Lissowska[25], N Szeszenia-Dabrowska[26], P Brennan[27], JD McKay[28], A Wright[29,30], PB Mitchell[29,30], JM Fullerton[31,32], PR Schofield[31,32], GW Montgomery[33], SE Medland[33], SD Gordon[33], NG Martin[33], V Krasnov[34], A Chuchalin[35], G Babadjanova[35], G Pantelejeva[36], LI Abramova[36], AS Tiganov[36], A Polonikov[37], E Khusnutdinova[38,39], M Alda[40,41], C Cruceanu[42,43,44], GA Rouleau[42], G Turecki[43,44,45], C Laprise[46], F Rivas[47], F Mayoral[47], M Kogevinas[48], M Grigoroiu-Serbanescu[49], P Propping[1], T Becker[5,12], M Rietschel[7], S Cichon[1,2,4,11], G Schratt[3] and MM Nöthen[1,2]

- Systematic analysis of common variants at all known microRNA loci, set-based testing adapted from VEGAS (Liu et al., 2010)
- Nine microRNAs showed significant association with BD including *miR-499*, *miR-708* and *miR-1908*
- Modification of miRNA dysregulation as a novel therapeutic approach?



Is the time of GWAS over?

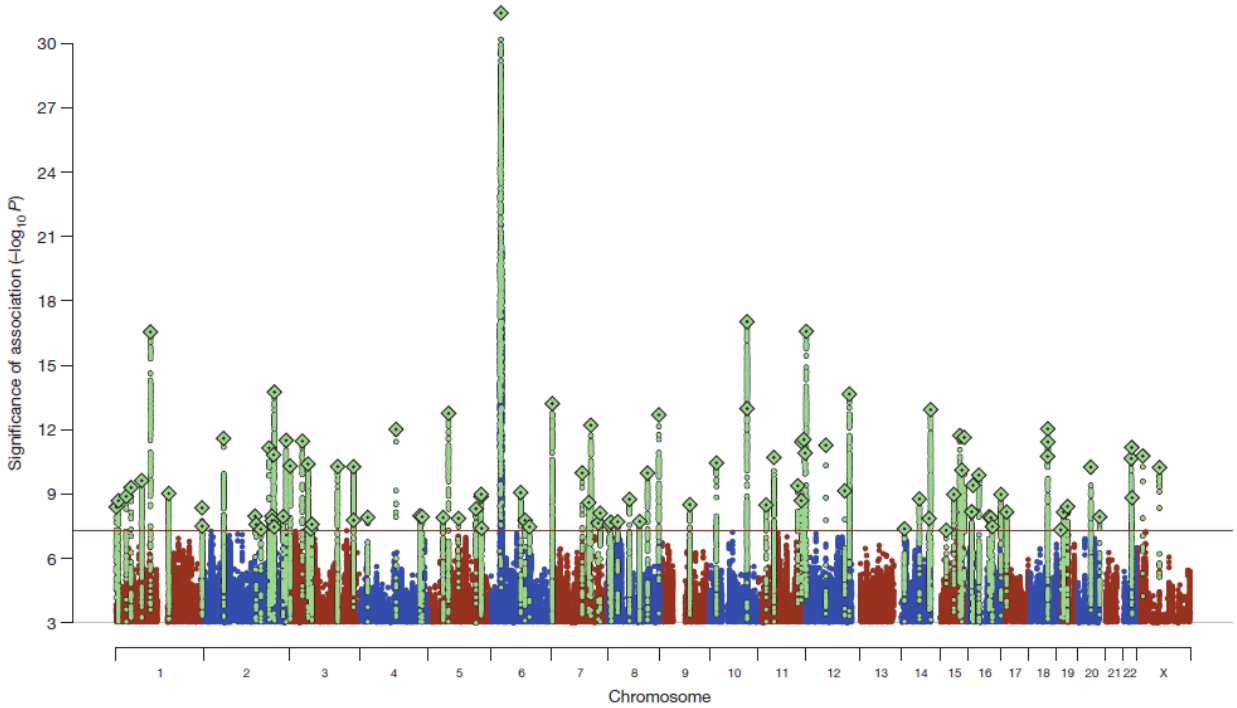
- Certainly not –
  SIZE MATTERS

ARTICLE

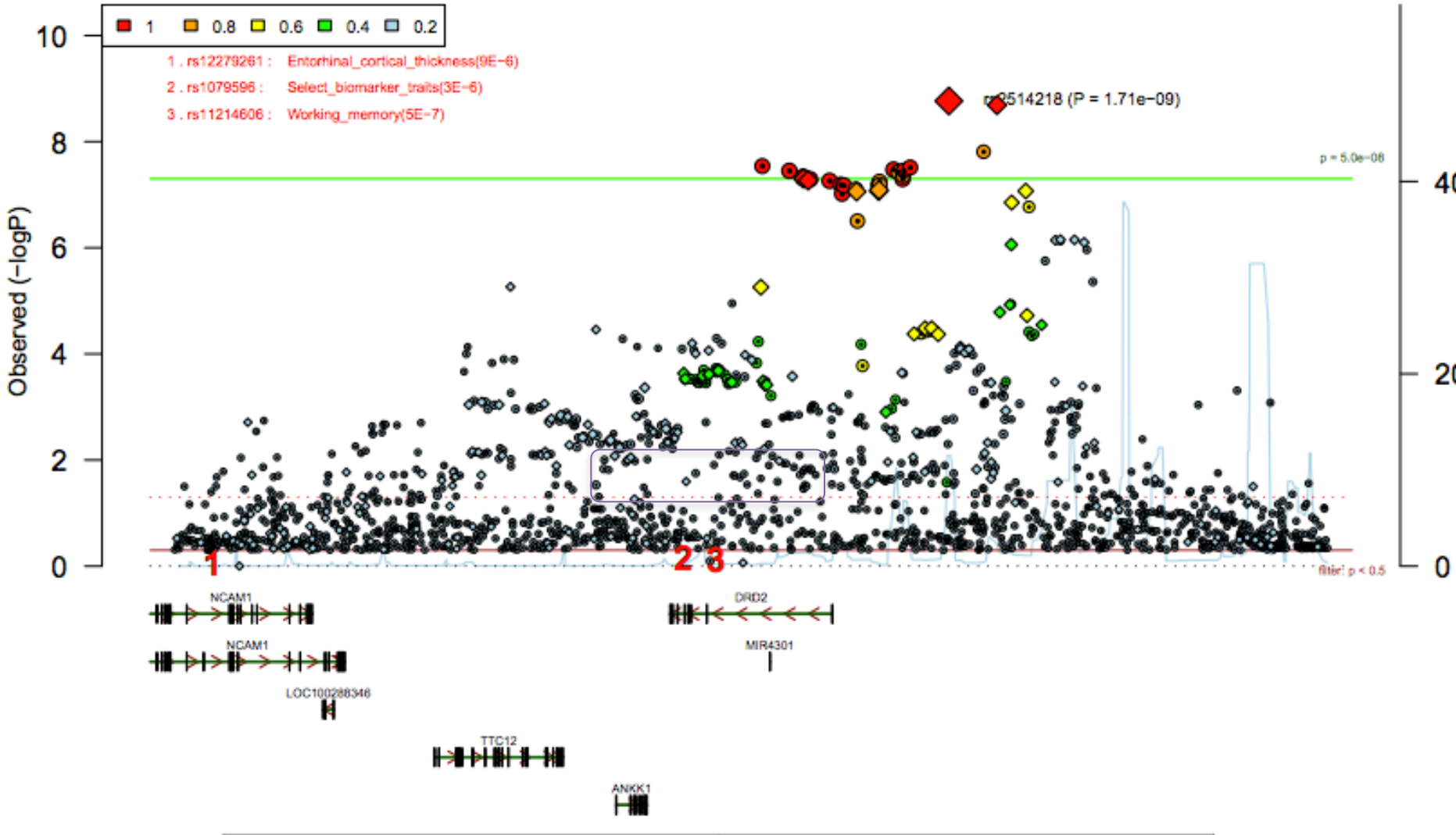
doi:10.1038/nature13595

Biological insights from 108 schizophrenia-associated genetic loci

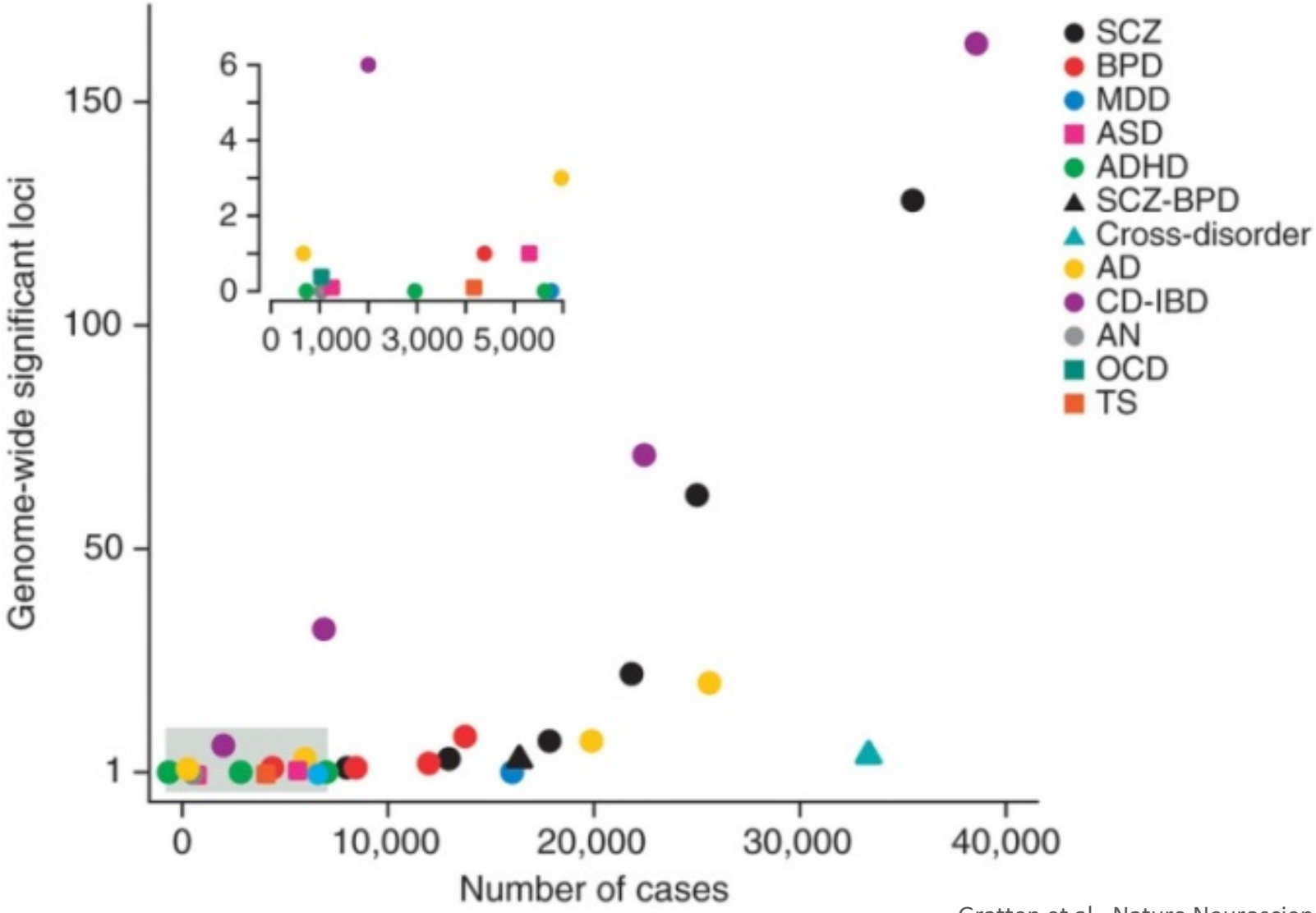
Schizophrenia Working Group of the Psychiatric Genomics Consortium*



DRD2 (neuroleptic drug target)

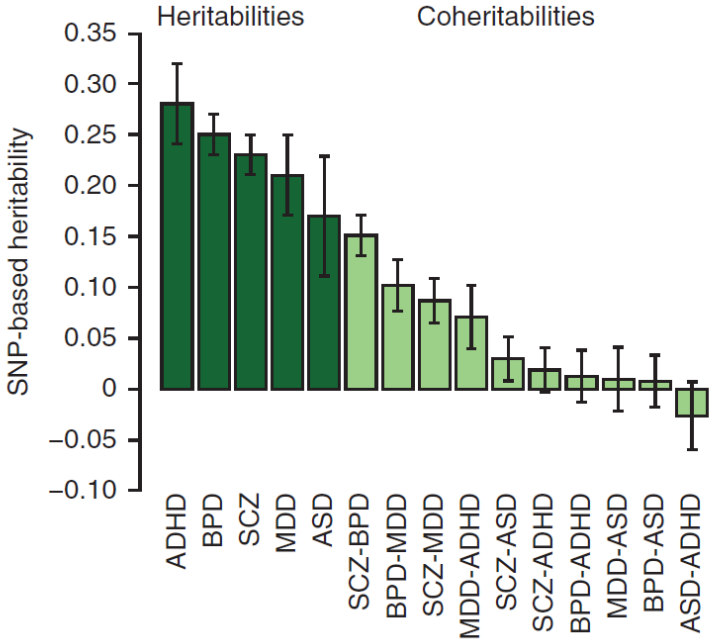


No. of gw-significant loci as a function of sample size



Gratten et al., Nature Neuroscience, 2014

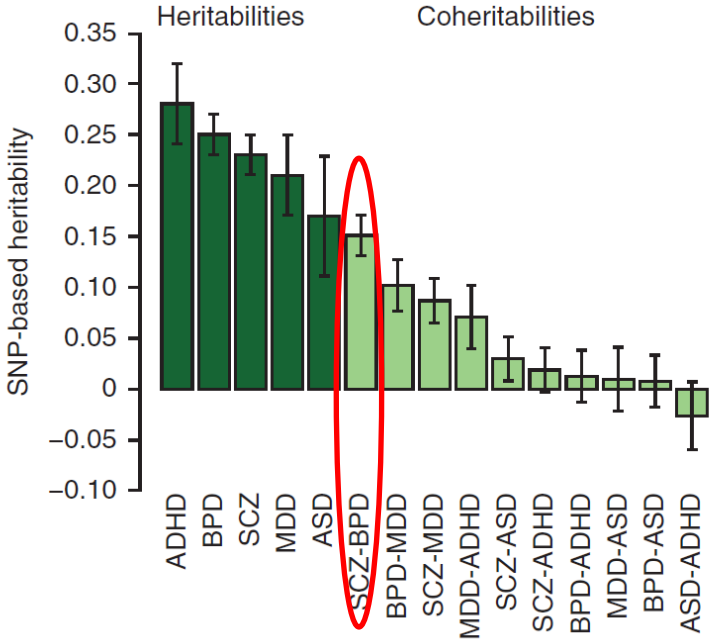
Genetic overlap of five common psychiatric disorders



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

- Bipolar disorder shows substantial clinical and genetic overlap with other psychiatric disorders
- High genetic correlation between BD and schizophrenia
- Research has not yet clarified what particular genes form the basis of this etiological overlap

Genetic overlap of five common psychiatric disorders



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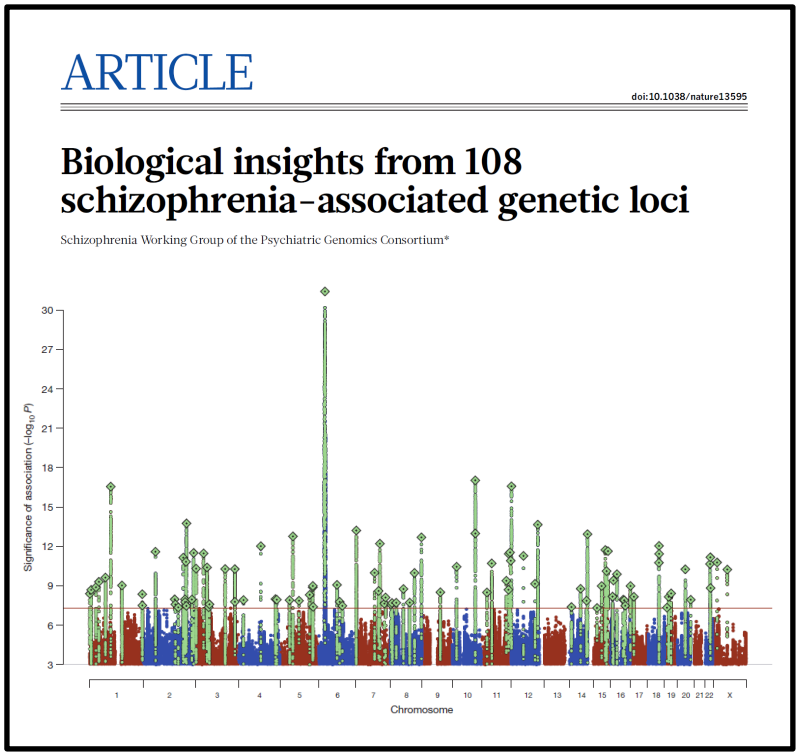
Combined GWAS of Bipolar disorder and schizophrenia

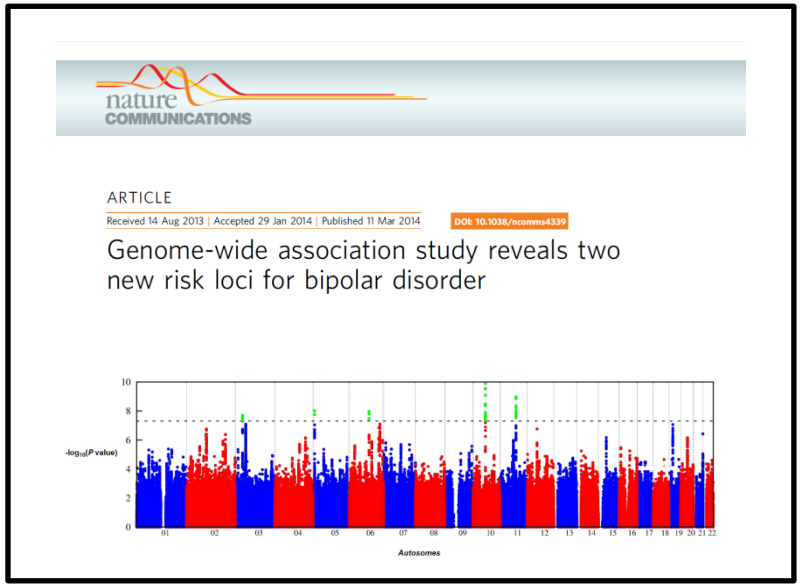


ARTICLE

doi:10.1038/nature13595

Biological insights from 108 schizophrenia-associated genetic loci

Schizophrenia Working Group of the Psychiatric Genomics Consortium*



nature COMMUNICATIONS

ARTICLE

Received 14 Aug 2013 | Accepted 29 Jan 2014 | Published 11 Mar 2014

DOI: 10.1038/ncomms4339

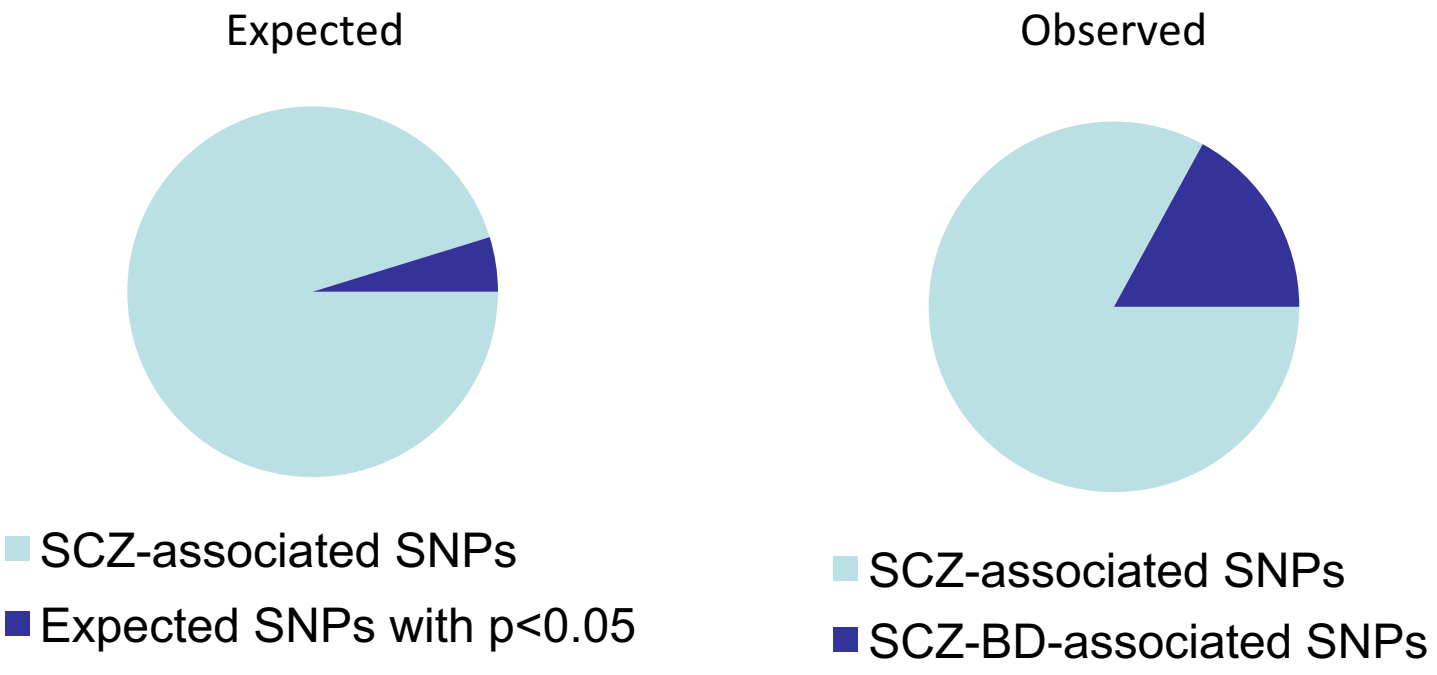
Genome-wide association study reveals two new risk loci for bipolar disorder

Schizophrenia Working Group of the PGC, Nature, 2014

Identification of shared risk loci and pathways

- Reimputation of our BD GWAS data, correction for shared controls

- 22 of 107 SCZ SNPs showed nominally significant association
- Significant enrichment of BD-associated SNPs within the known SCZ-associated loci ($p=1.46x10^{-8}$)



Top SCZ-BD associated SNPs

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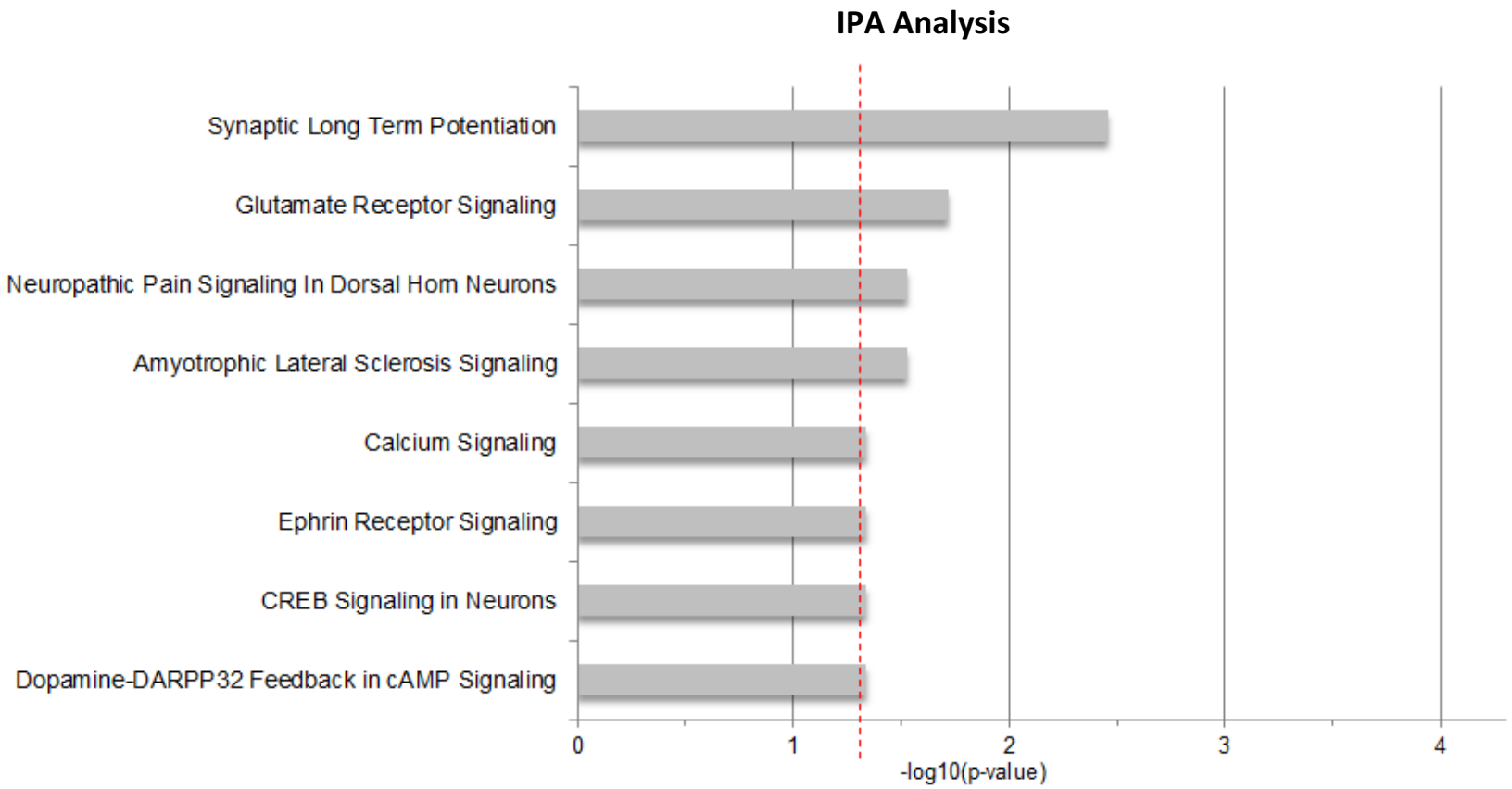
SNP	Chr	Position	Alleles	P MooDS	P PGC BD	P BD Meta	P PGC SCZ	Plausible Gene/s
rs75968099	3	36858583	T/C	0.0023	1.06×10^{-5}	8.84×10^{-8}	1.05×10^{-13}	*TRANK1*
rs2535627	3	52845105	C/T	0.0452	1.93×10^{-6}	3.32×10^{-7}	4.26×10^{-11}	*ITIH3-ITIH4*
rs140505938	1	150031490	T/C	0.0398	0.00132	0.00014	4.49×10^{-10}	*VPS45*
rs6704641	2	200164252	A/G	0.0365	0.00160	0.00015	8.33×10^{-9}	*SATB2*
rs7893279	10	18745105	G/T	0.0042	0.00801	0.00017	1.97×10^{-12}	*CACNB2*
rs6704768	2	233592501	A/G	0.0141	0.00546	0.00026	2.32×10^{-12}	*GIGYF2*
rs12704290	7	86427626	A/G	0.0023	0.02227	0.00039	3.33×10^{-10}	*GRM3*
rs3735025	7	137074844	C/T	0.4438	0.00047	0.00072	3.28×10^{-9}	*DGKI*
rs211829	7	110048893	C/T	0.0438	0.00703	0.00080	3.71×10^{-8}	-
rs324017	12	57487814	C/A	0.1323	0.00288	0.00088	2.13×10^{-8}	*NAB2*
rs2909457	2	162845855	A/G	0.0745	0.00526	0.00093	4.62×10^{-8}	*SLC4A10-DPP4*
rs9922678	16	9946319	A/G	0.1932	0.00209	0.00096	1.28×10^{-8}	*GRIN2A*

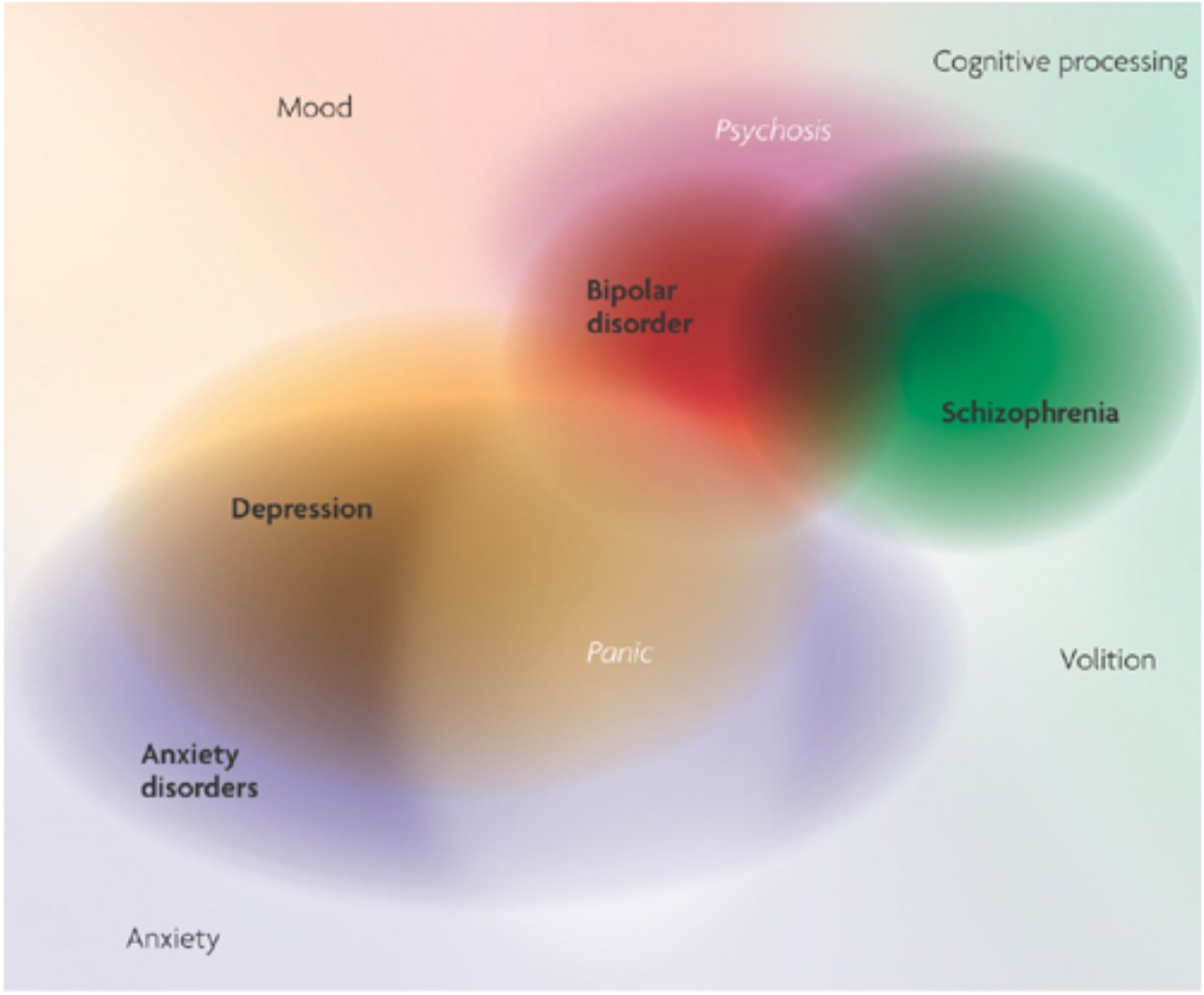
Results of the pathways analyses



What GWAS have added to our knowledge

- There is a significant polygenic contribution of common variants to BD and SCZ; small genetic effects (OR <1.2)
- Substantial overlap of common risk factors (60%) contributing to BD and SCZ
- Cumulative impact of common alleles explain about 25-28% of the phenotypic variance for BD, about 23-25% for SCZ
- Disease pathways are beginning to emerge: Neurodevelopment, Ca++/Glu Signalling, immune processes ……
- GWAS have the potential to identify drug targets (DRD2 is detected by GWAS)

Further important use of GWAS results: Reverse phenotyping to re-classify psychiatric disorders



Nature Reviews | Genetics

NCAN Reverse Phenotyping Approach

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Universitätsspital Basel

641 Bipolar Disorder	597 Schizophrenia	480 Major Depression

Principal component analysis of 69 clinical lifetime symptoms (OPCRIT)

↓

Five factor solution in the combined and single patient sample

Reality distortion
Mania
Depression
(Disorganization)
Drug abuse/dependence

rs1064395 risk allele carriers display higher *mania* factor scores (p_{corr}=0.045), in particular *overactivity* scores (p_{corr}=0.005)

Miro, Meier *et al*. (2012) Am J Psychiatry

Ncan$^{-/-}$ mice: phenotyping

Previous investigation of Ncan$^{-/-}$ mice:
normal development, anatomy, and general performance, possible mild effect on hippocampal LTP

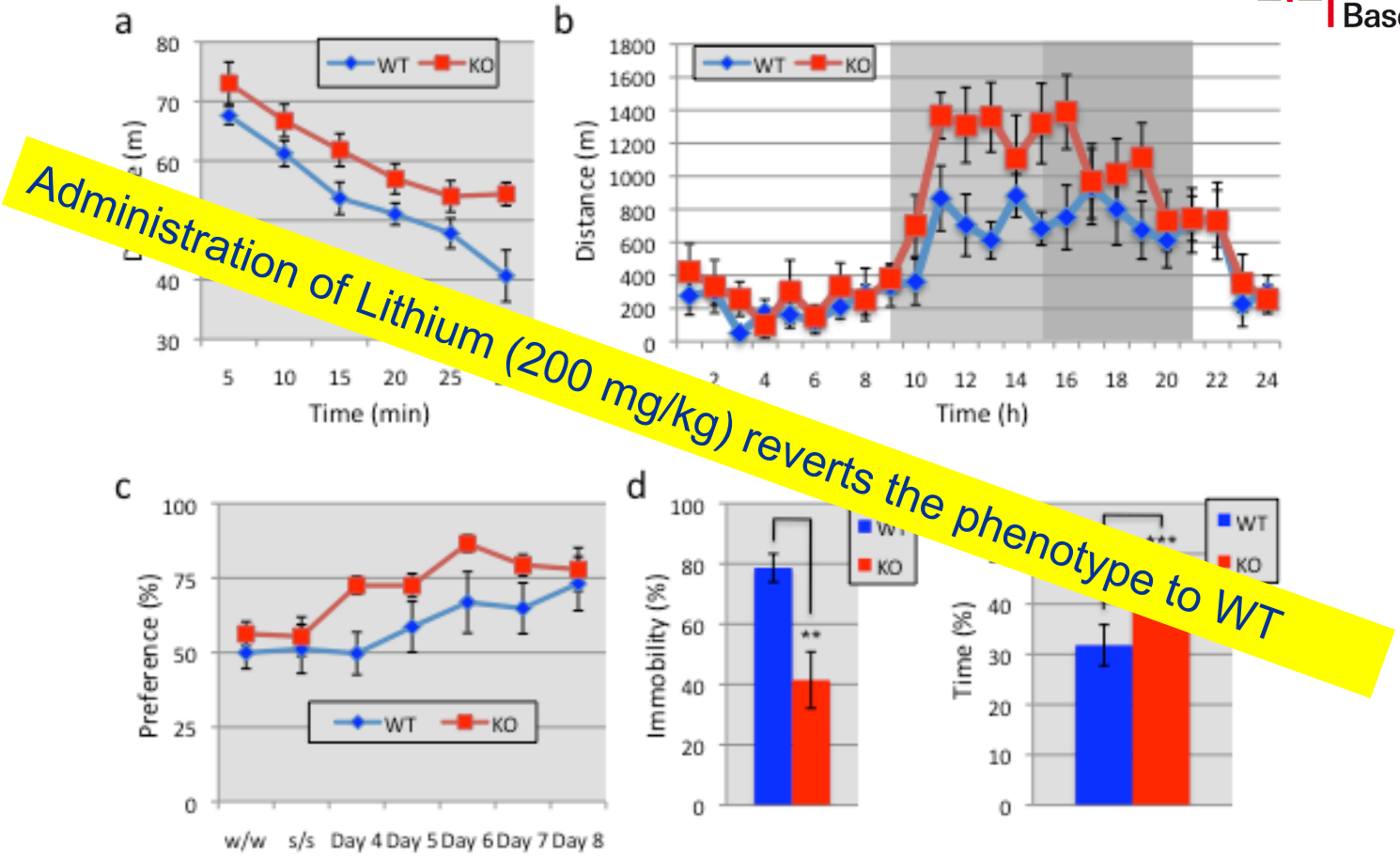
Ncan$^{-/-}$ were subjected to a range of behavioral tests

- Open field activity
- Home cage activity
- Porsolt forced swim test
- Elevated plus maze
- Elevated zero maze
- Saccharin preference
- Marble burying
- Sensitivity to amphetamine
- Pre-pulse inhibition

Behavioral abnormalities observed in the Ncan$^{-/-}$ mice were tested for sensitivity to treatment with lithium.

Miró, Meier et al., Am J Psychiatry 2012

Ncan$^{-/-}$ mice display mania-like behaviour



a) Locomotor activity in an open-field arena
b) Home cage locomotor activity
c) Saccharine preference
d) Immobility time in Porsolt forced swim test
e) Time spent in open arm

Miró, Meier et al., Am J Psychiatry 2012

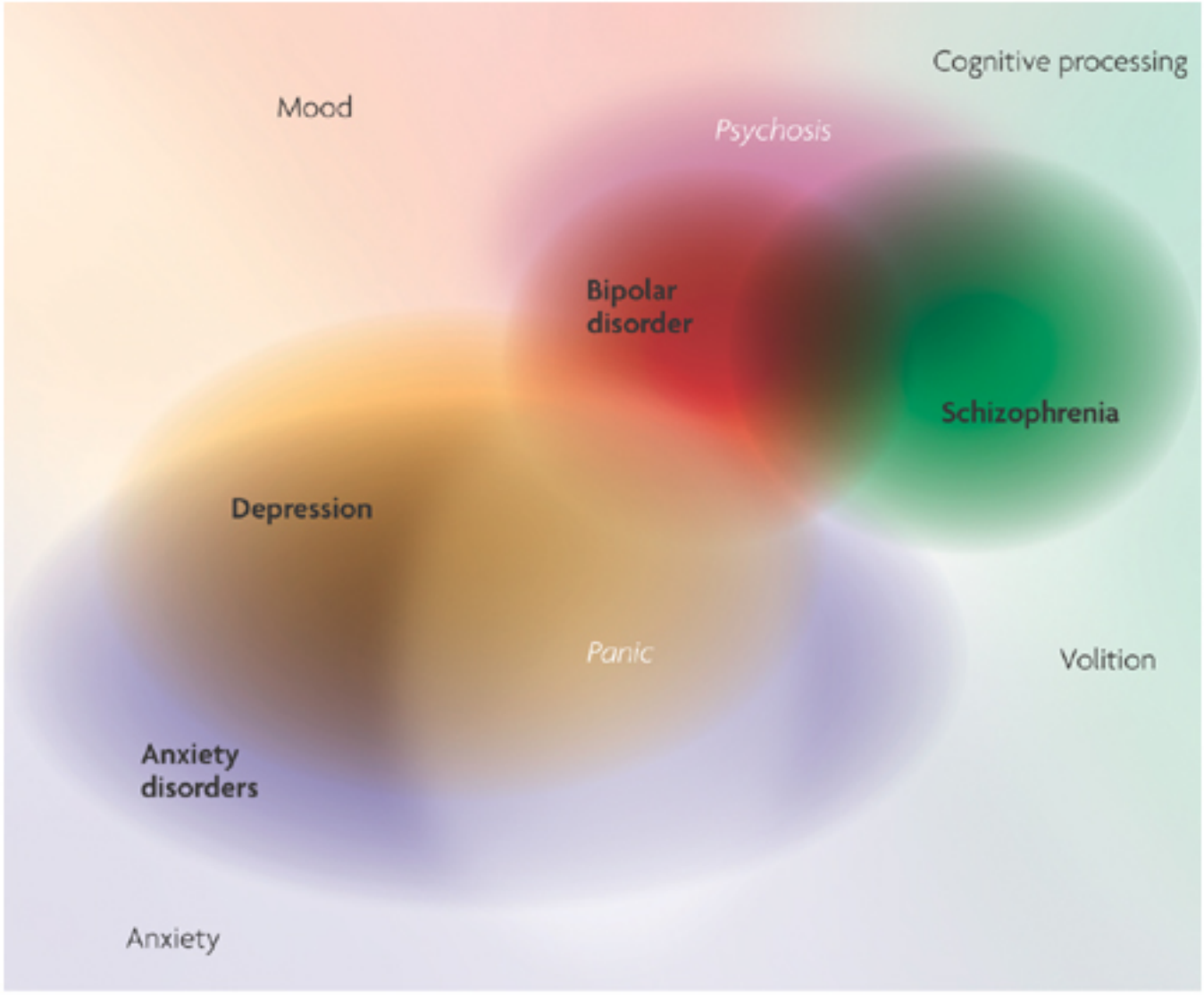
From genetic association to mouse model

The finding in the human phenotype is strikingly similar to the behavioral phenotype observed in Ncan-/- mice.

Ncan deficient mice may serve as a novel genetic animal model for mania.

The treatment and prophylaxis of mania overactivity symptoms is a challenging aspect of clinical management, as patients with these symptoms typically lack insight, and the negative social- and financial consequences of their reckless behavior are often long-term.

Use of reverse phenotyping (SNPs or polygenic risk scores) for disease classification: nosology informed by disease cause



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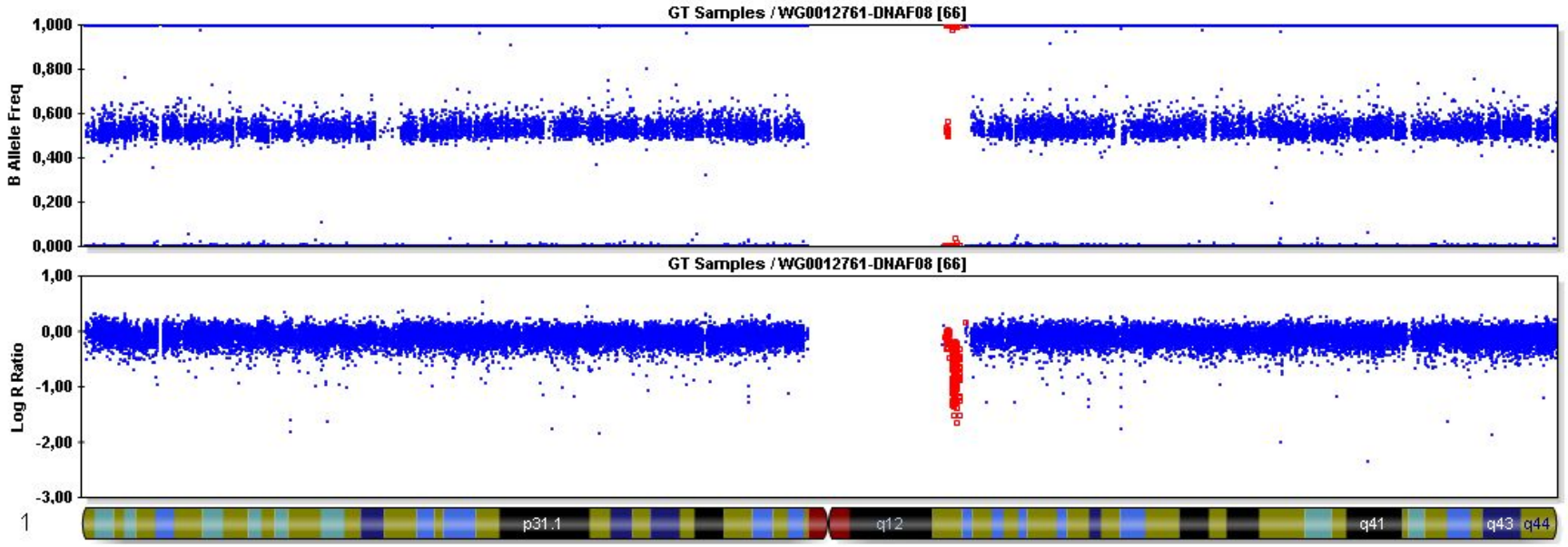
What about rare variants?

- Models of illness most consistent with a polygenic contribution of common and rare variants
- Common variants explain only part (25-30%) of the phenotypic variability. What explains the rest?
- Rare variants may well make a significant contribution to disease (↑ ORs, cumulative effect)
- Some genes may only show rare risk variants and may completely escape detection with GWAS
- A first window to the existence of rare variants were CNVs
- Now NGS-based sequencing

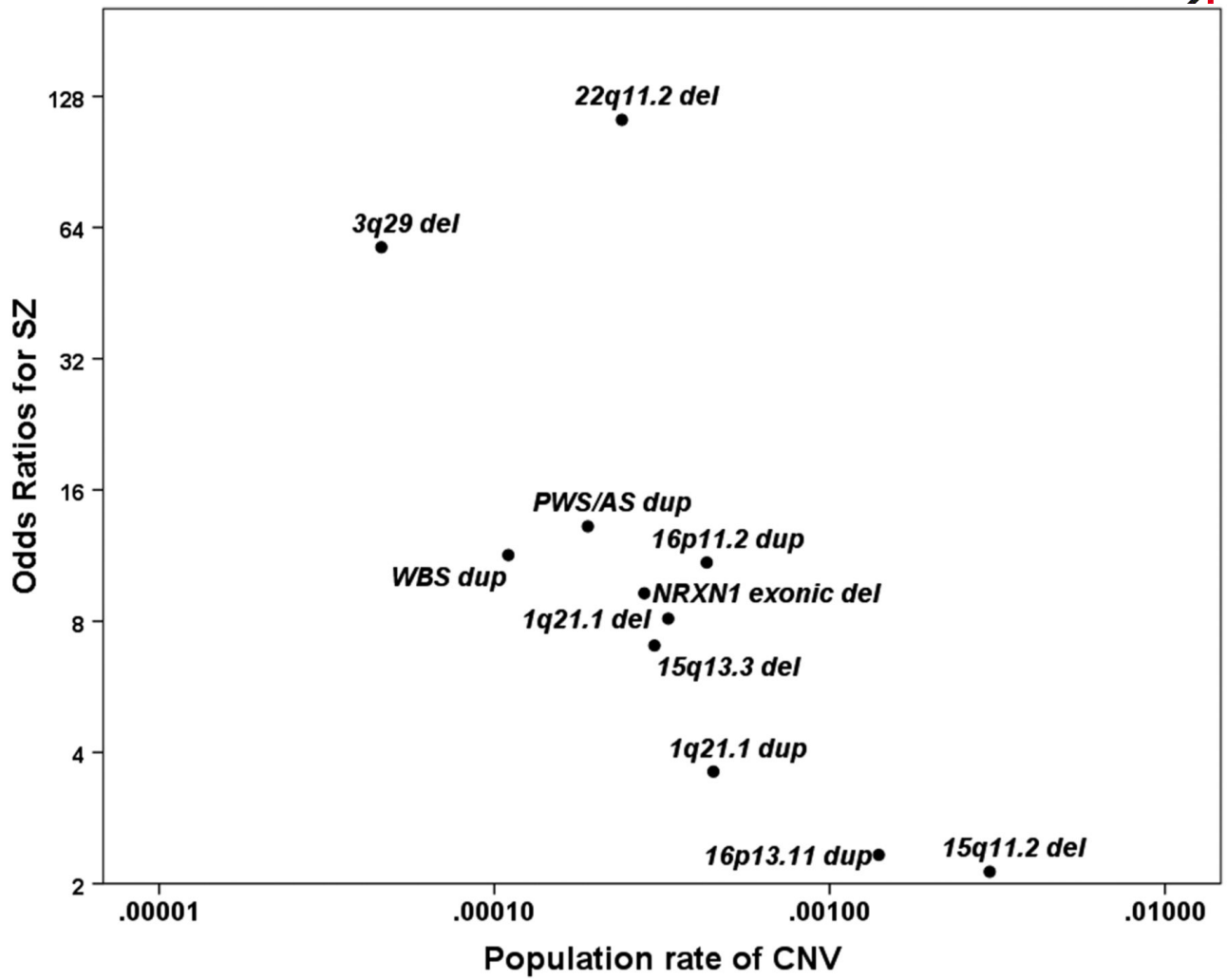
1q21 Microdeletion associated with schizophrenia (4,200 patients, 39,800 controls: OR=14,83)



Stefansson*, Rujescu*, Cichon* et al., Nature (2008)

Contribution of rare CNVs to schizophrenia

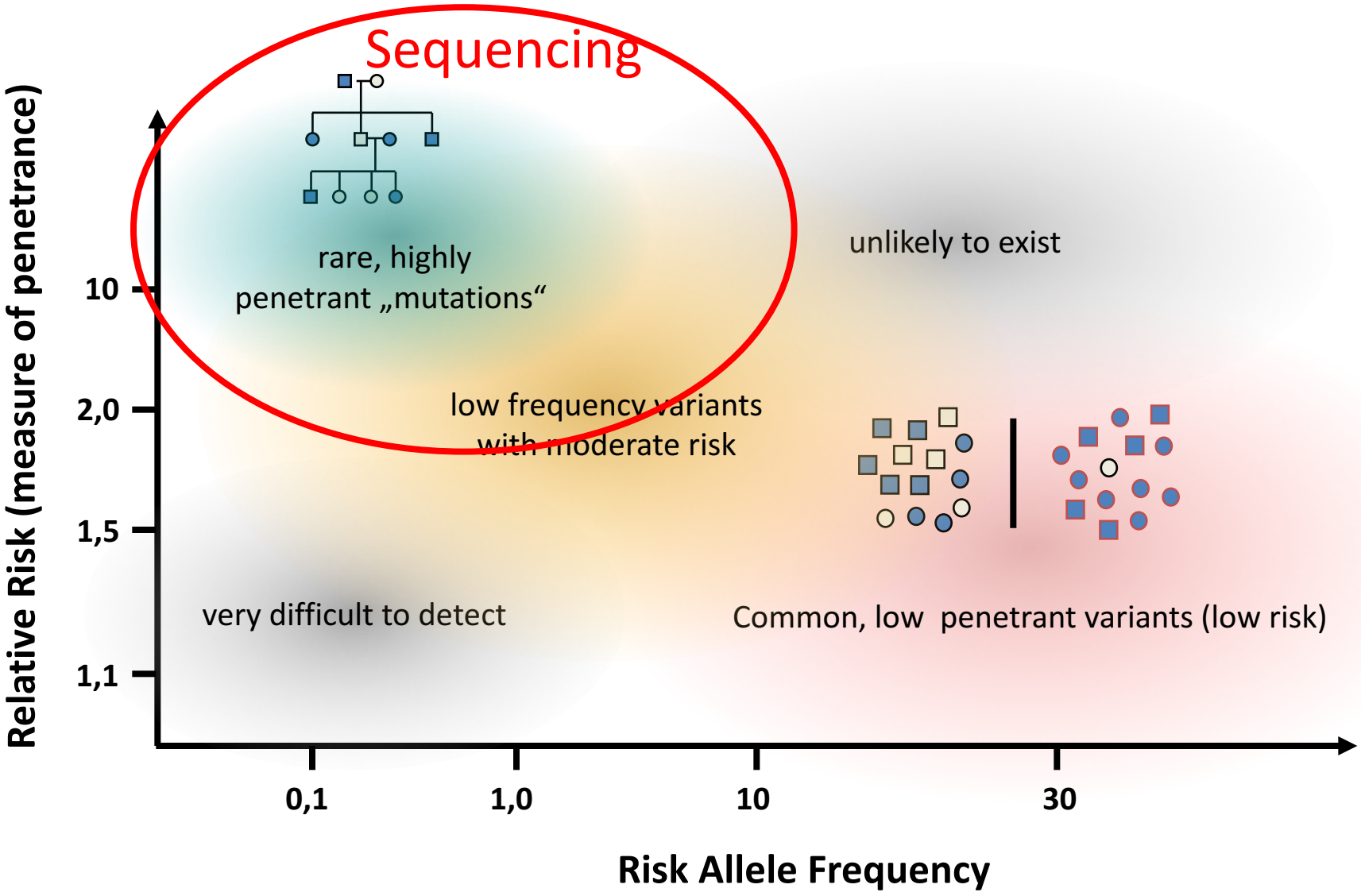
Correlation between population rates and ORs for schizophrenia



George Kirov Hum. Mol. Genet. 2015;24:R45-R49

Human Molecular Genetics

Identification of rare variants by sequencing



Promising early example for low freq. variants of higher penetrance in BD

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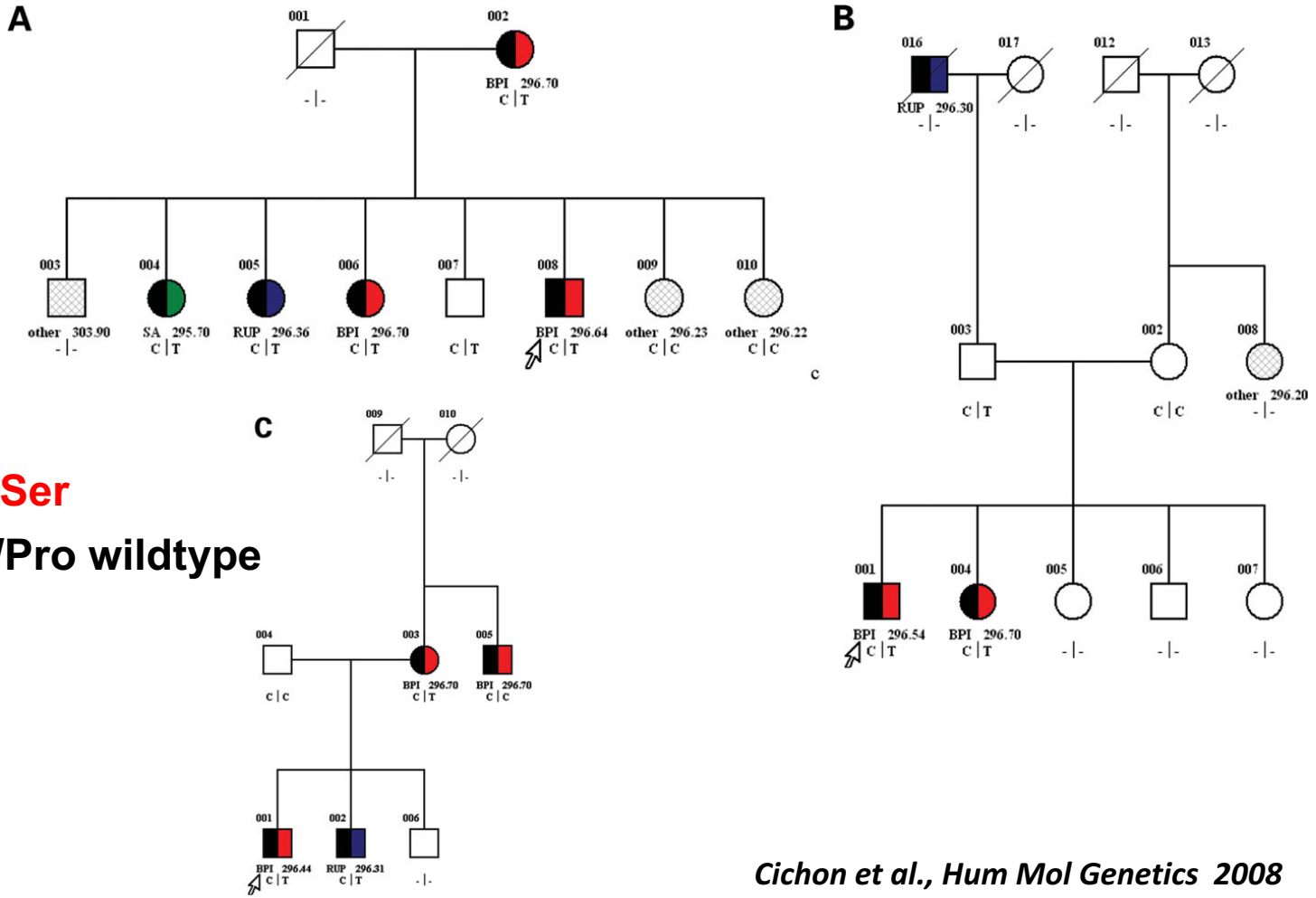
Identification of Tryptophan hydroxylase P206S; MAF: 0.02, by candidate gene re-sequencing; evidence for involvement in Bipolar Disorder:



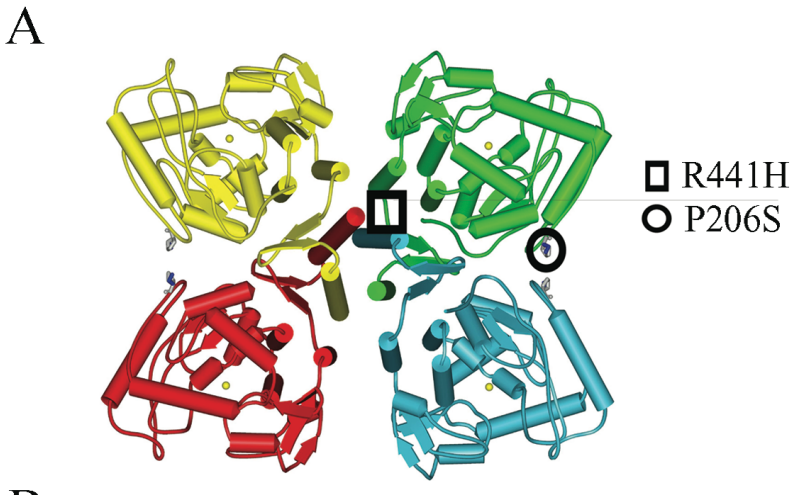
CT Pro/Ser

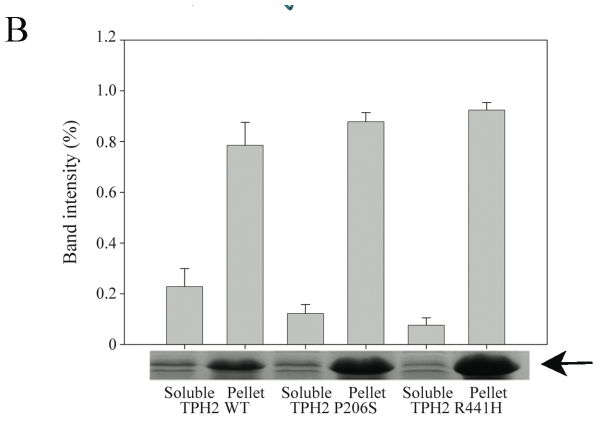
CC Pro/Pro wildtype

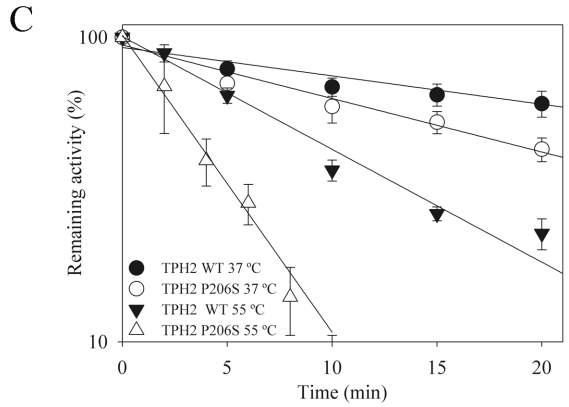
Cichon et al., Hum Mol Genetics 2008

Functional studies of TPH2 variant P206S

(collab. with Jan Haavik, U. Bergen/Norway)







Decreased stability and solubility of TPH2 206S
=>reduced serotonin production in the brain (fits with observations in depressive patients and suicide victims)

Cichon et al., Hum Mol Genetics 2008

Recruitment of families with BD in Andalusia (M. Rietschel / M. Nöthen)

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Currently WES in 27 families (3 / family)

(Collaboration within INTEGRAMENT project between Bonn and Basel)

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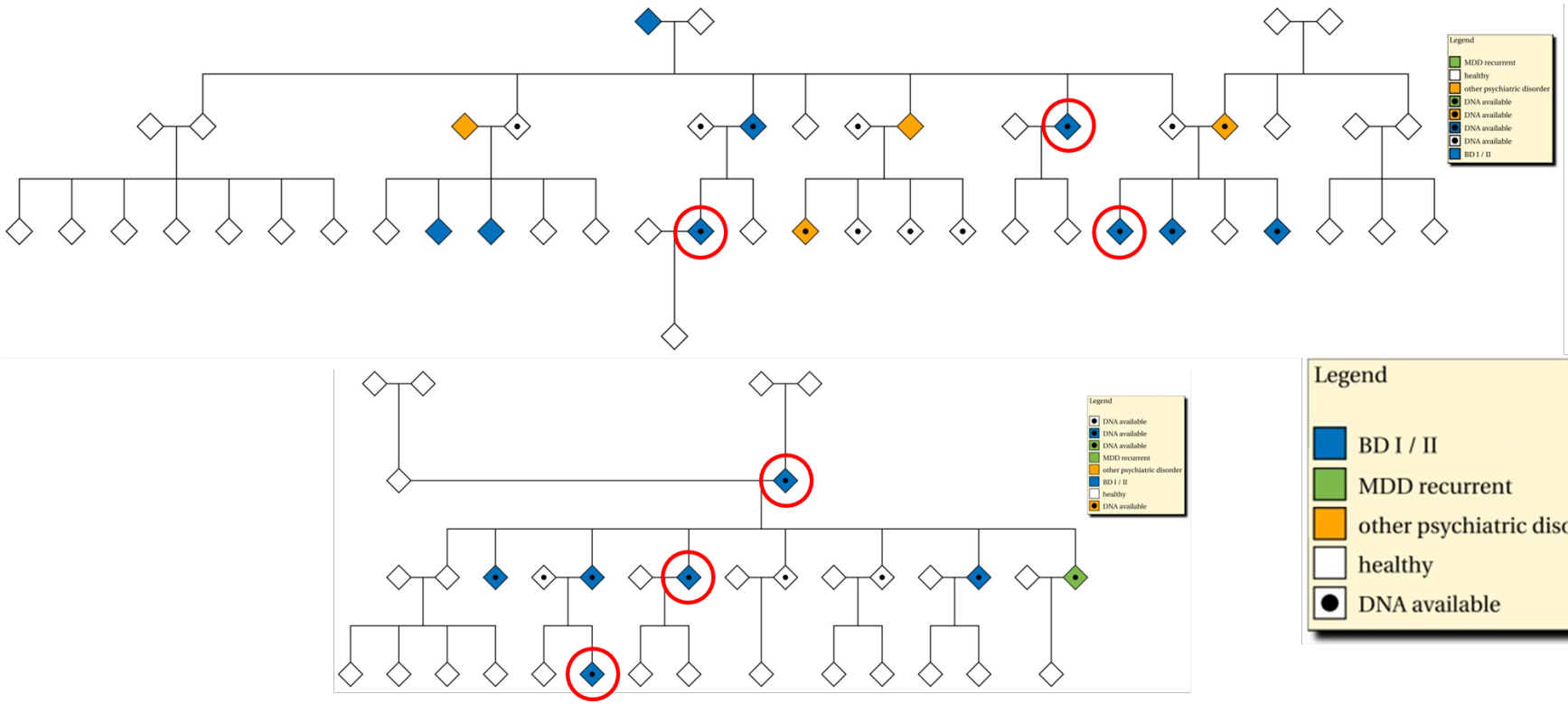
At least 3 affected individuals

Pedigrees most densely affected with bipolar disorder (but also SCZ, SA, MDD)

All affected individuals in one branch of the family



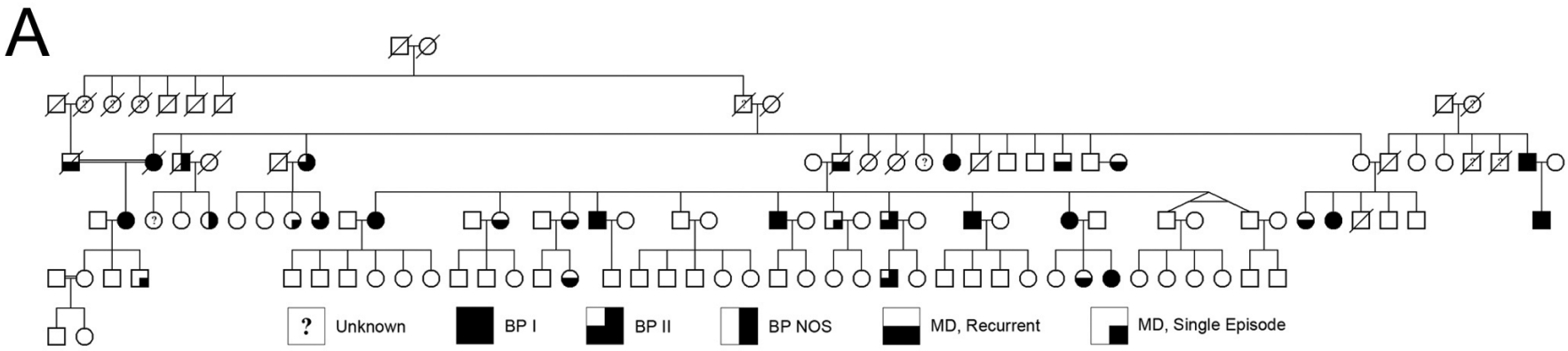
Forstner, Fischer et al., in preparation

Currently whole exome seq. in 20 families (10 ind. / family)
(SNF project Basel)

Sequence larger number of affecteds (and unaffecteds) in extended pedigrees

Based on experience from myocard infarction study (Erdmann et al., Nature 2013) => digenic effects

Increased chances to overcome problems posed by „phenocopies“



Functional perspectives: what's needed to fully understand the biological processes influenced by risk variants?

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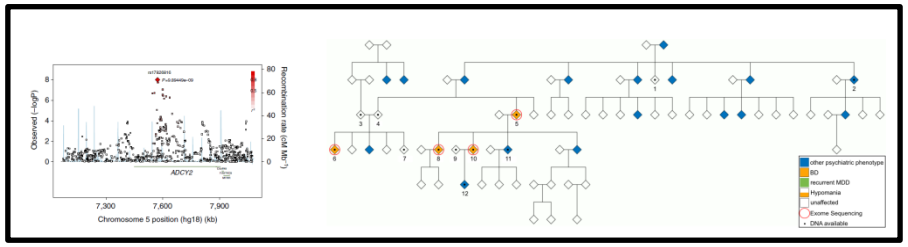
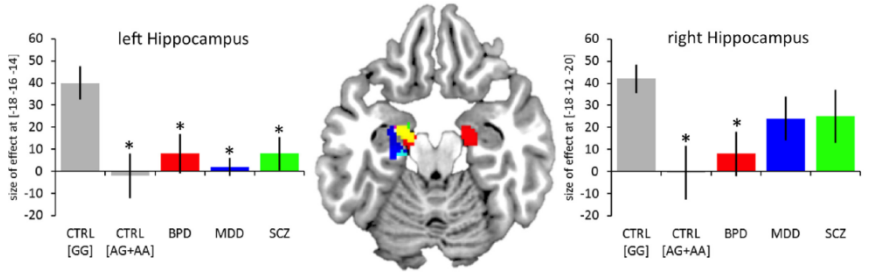
- functional studies (animal models, iPSC, etc.)
  (=> collaboration with Life&Brain Center at Univ. of Bonn)

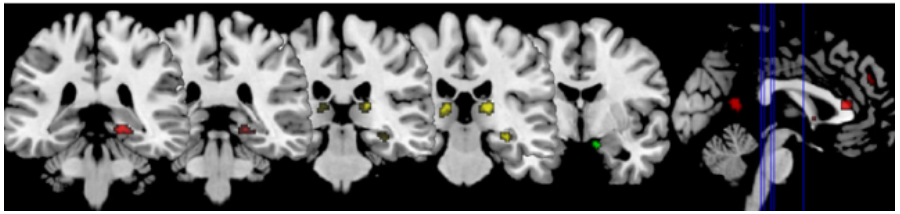


- better molecular maps of individual brain cells and brain regions (eQTLs/meQTLS)
  (=> research group "Genomic Imaging" at Research Center Jülich; member of Human Brain Project)



Erk et al., Biol Psychiatry, 2014

- imaging studies to elucidate the impact of associated variants
  (=> research group "Genomic Imaging" at Research Center Jülich; member of Human Brain Project)



Krug et al., Schizophr Bull, 2013

The more genetic factors are known...
also investigate gene-environment interaction

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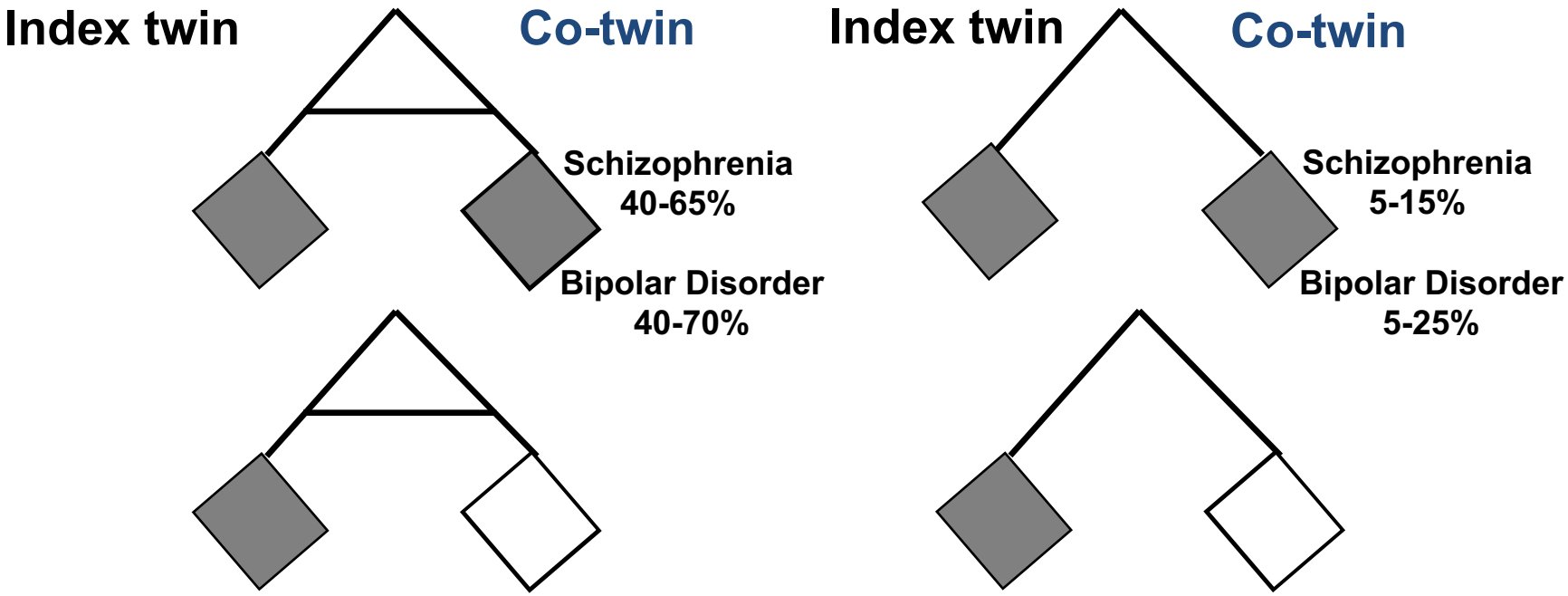
Monozygotic twins

Dizygotic twins



Heritability Estimates
~ 60-80%

PNAS

Epigenetic differences arise during the lifetime of monozygotic twins

Mario F. Fraga*, Esteban Ballestar*, Maria F. Paz*, Santiago Ropero*, Fernando Setien*, Maria L. Ballestar†, Damia Heine-Suñer‡, Juan C. Cigudosa§, Miguel Urioste¶, Javier Benitez¶, Manuel Boix-Chornet†, Abel Sanchez-Aguilera†, Charlotte Ling‖, Emma Carlsson‖, Pernille Poulsen**, Allan Vaag**, Zarko Stephan††, Tim D. Spector††, Yue-Zhong Wu‡‡, Christoph Plass‡‡, and Manel Esteller*§§

*Epigenetics, §Cytogenetics, and ¶Genetic Laboratories, Spanish National Cancer Centre (CNIO), Melchor Fernandez Almagro 3, 28029 Madrid, Spain; †Department of Behavioral Science, University of Valencia, 46010 Valencia, Spain; ‡Molecular Genetics Laboratory, Genetics Department, Son Dureta Hospital, 07014 Palma de Mallorca, Spain; ‖Department of Clinical Sciences, University Hospital Malmö, Lund University, S-205 02 Malmö, Sweden; **Steno Diabetes Center, 2820 Gentofte, Denmark; ††Twin Research and Genetic Epidemiology Unit, St. Thomas' Hospital, London SE1 7EH, United Kingdom; and ‡‡Human Cancer Genetics Program, Department of Molecular Virology, Immunology, and Medical Genetics, Ohio State University, Columbus, OH 43210

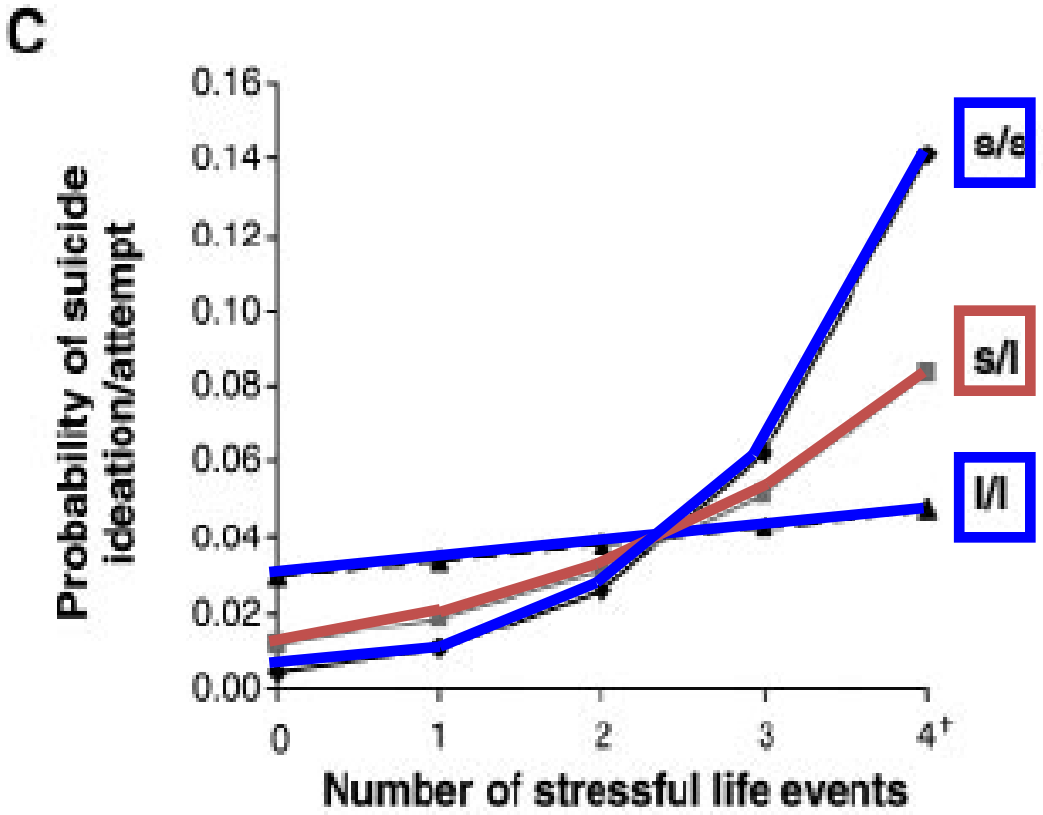
Edited by Stanley M. Gartler, University of Washington, Seattle, WA, and approved May 23, 2005 (received for review January 17, 2005)

Monozygous twins share a common genotype. However, most monozygotic twin pairs are not identical; several types of phenotypic discordance may be observed, such as differences in susceptibilities to disease and a wide range of anthropomorphic features. There are several possible explanations for these observations, but one is the existence of epigenetic differences. To address this issue, we examined the global and locus-specific differences in DNA methylation and histone acetylation of a large cohort of monozygotic twins. We found that, although twins are epigenetically indistinguishable during the early years of life, older monozygous twins exhibited remarkable differences in their overall content and genomic distribution of 5-methylcytosine DNA and histone acetylation, affecting their gene-expression portrait. These findings indicate how an appreciation of epigenetics is missing from our understanding of how different phenotypes can be originated from the same genotype.

Materials and Methods

Subjects. Eighty volunteer Caucasian twins from Spain were recruited in the study, including 30 male and 50 female subjects. Their mean (±SD) age was 30.6 (±14.2) years (range, 3–74 years). Twins studied included monochorionic and dichorionic. All subjects, or in the case of children, the parents, gave their informed written consent to be included in the study. Lymphocyte cells were purified by standard procedures and stored at −80°C. In eight cases, epithelial skin cells were obtained from buccal smears. Muscle biopsy tissues ($n = 14$) from the vastus lateralis muscle and s.c. abdominal tissue ($n = 4$) were obtained by needle suction under local anesthesia from volunteer MZ twins from Denmark and the United Kingdom, respectively. Homozygosity was determined by using highly polymorphic short tandem-repeat loci. With five markers, the probability that any twin pair was MZ if all markers were concordant was 99% (5).

Genetic and Environmental Factors
Additive and/or Interacting (with Serotonin transporter variant)



Caspi et al. 18 JULY 2003 VOL 301 SCIENCE www.sciencemag.org

Stressful life events- risk factor for psychiatric disorders

- **Poverty**
- **Unemployment**
- **Social inequality**
- **Migration**
- **Urban living**
- **Traumatization**

The Bo-Ma-Ba connection

Basel

Andreas Forstner

Markus Nöthen

universitäts klinikum bonn
Institut für Humangenetik

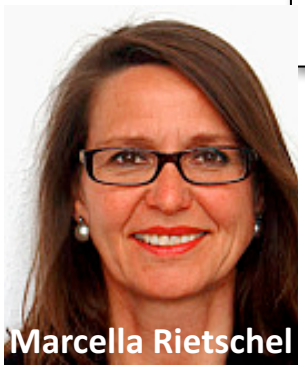
life&brain

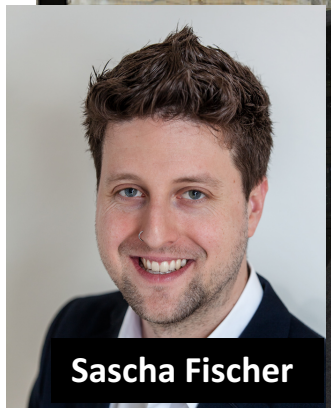
UNI BASEL


Per Hoffmann

University of Bonn
Inst. Human Genetics; Dept. Genomics; Life&Brain
Nöthen/Cichon/Forstner/Degenhardt
Mühleisen/Hoffmann/Herms/Proppimg

Central Institute of Mental Health, Mannheim
Rietschel/Strohmeier/Witt/Treutlein/Frank/
(Schulze)


Marcella Rietschel


Sascha Fischer

Stefan Herms

University of Basel
Human Genomics; Dept. of Biomedicine
Cichon/Hoffmann/Herms/Reinbold/Fischer