Psychiatric genetics 2025: the need to focus on childhood, adolescence, and life

Thomas G. Schulze, MD

Institute of Psychiatric Phenomics and Genomics (IPPG), Ludwig-Maximilians-University Munich, Germany

LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN — CAMPUS INNENSTADT — INSTITUT FÜR PSYCHIATRISCHE PHÄNOMIK UND GENOMIK — IPPG

Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University, Baltimore, MD, USA

JOHNS HOPKINS UNIVERSITY

Outline

1. Where are we today?
2. Where would we like to be in 2025?
3. How can we get there? Think trajectories!

Where are we today?

Genetics of psychiatric disorders: a story of complexity

- 20th century: family, twin, and adoption studies
- Psychiatric disorders are highly heritable (~40 % major depression, ~70 % schizophrenia, ~80 % bipolar disorder)
- Genetic linkage and association studies
- Inconsistency of findings
- 20st century: larger samples, genome-wide approaches

Genomic approaches

- 20th century: gen**eti**cs
- 21st century: gen**omi**cs
- Big data & novel, powerful molecular tools
- Case-control studies in thousands and tens of thousands of samples: genome-wide asociation studies (GWAS)
- Stringent significance thresholds: $p < 5 \times 10^{-8}$

Genomic approaches

International consortia for genomic approaches

Psychiatric Genomics Consortium

Home

Home
Twitter
Results
- Results to date
- ADHD
- Bipolar disorder
- Cross-disorder
- MDD
- Schizophrenia
- Background papers

Data Sharing
- Data visualization
- Obtaining results
- "Open-source" philosophy
- Funder perspectives
- Intellectual property

Scientific Plan
- Scope
- pgc1
- pgc2

For Investigators
- Uploading Information

What Is The PGC?

The purpose of the Psychiatric Genomics Consortium (PGC) is to conduct meta-analyses of genome-wide genetic data for psychiatric disease. This website provides information about the organization, implementation, and results of the PGC.

The basic idea is that individual studies are generally too small to identify robust and replicable associations. Meta-analysis is a widely-used technique that can combine information across studies.

The PGC began in early 2007, and quickly became a confederation of most investigators in the field. PGC papers typically have over 200 authors. PGC scientists are from over 60 institutions in 19 countries. This is the largest consortium in the history of psychiatry, and the largest biological experiment in the field.

From 2007-11, the PGC has focused on five critically-important disorders: autism, attention-deficit hyperactivity disorder, bipolar disorder, major depressive disorder, and schizophrenia. In 2013, we added anorexia nervosa, OCD/Tourette's, and PTSD.

The initial intent of the PGC was to investigate the common single nucleotide polymorphisms (SNPs) genotyped on commercial arrays. The focus has expanded to include structural variation (copy number variation) and uncommon or rare genetic variation.

The PGC has received funding from many sources. Before participation in the PGC, establishing and genotyping of the primary case-control collections were funded by a wide range of national, international, and commercial funders. Funding for the PGC was for data analytical efforts. The PGC has relied heavily on the goodwill of its members and their donated effort. We are deeply grateful to the National Institute of Mental Health (NIMH) , the Netherlands Genetic Cluster Computer, Hersenstichting Nederland, and One Mind for Research for their sponsorship of the PGC.

Genomic approaches

Genome-wide asscciation studies (GWAS) for the identification of common variants in large samples

ARTICLE

doi:10.1038/nature13595

Biological insights from 108 schizophrenia-associated genetic loci

Schizophrenia Working Group of the Psychiatric Genomics Consortium*

Schizophrenia is a highly heritable disorder. Genetic risk is conferred by a large number of alleles, including common alleles of small effect that might be detected by genome-wide association studies. Here we report a multi-stage schizophrenia genome-wide association study of up to 36,989 cases and 113,075 controls. We identify 128 independent associations spanning 108 conservatively defined loci that meet genome-wide significance, 83 of which have not been previously reported. Associations were enriched among genes expressed in brain, providing biological plausibility for the findings. Many findings have the potential to provide entirely new insights into aetiology, but associations at *DRD2* and several genes involved in glutamatergic neurotransmission highlight molecules of known and potential therapeutic relevance to schizophrenia, and are consistent with leading pathophysiological hypotheses. Independent of genes expressed in brain, associations were enriched among genes expressed in tissues that have important roles in immunity, providing support for the speculated link between the immune system and schizophrenia.

Genomic approaches

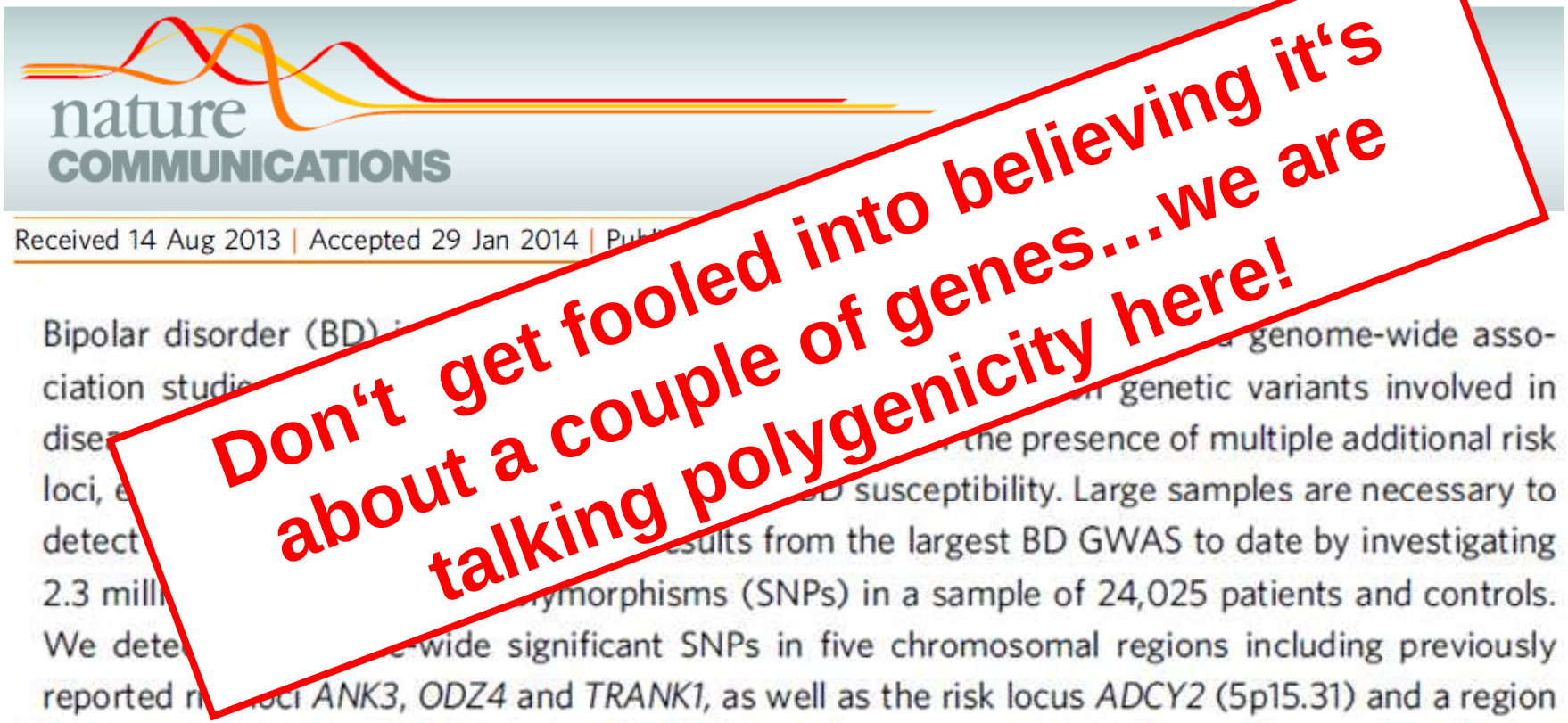
Genome-wide asscciation studies (GWAS) for the identification of common variants in large samples

	Single nucleotide polymorphism	Study	p value	Odds ratio	Nearest gene(s)
BD	rs12576775	PGC-BD[33]	$4{\cdot}4\times10^{-8}$	1·14	*ODZ4*
BD	rs4765913	PGC-BD[33]	$1{\cdot}5\times10^{-8}$	1·14	*CACNA1C*
BD	rs1064395	Cichon et al[30]	$2{\cdot}1\times10^{-9}$	1·17	*NCAN*
BD	rs7296288	Green et al[35]	$9{\cdot}0\times10^{-9}$	0·90	*RHEBL1, DHH*
BD	rs3818253	Green et al[35]	$3{\cdot}9\times10^{-8}$	1·16	*TRPC4AP*
BD	rs9371601	Green et al[38]	$2{\cdot}9\times10^{-8}$	1·10	*SYNE1*
BD+SZ	rs1344706	O'Donovan et al[39]	$4{\cdot}1\times10^{-13}$	1·11	*ZNF804A*
BD+SZ	rs2239547	PGC SZ[40]	$7{\cdot}8\times10^{-9}$	1·12	*ITIH3-ITIH4*
BD+SZ	rs10994359	PGC SZ[40]	$2{\cdot}4\times10^{-8}$	1·22	*ANK3*
BD+SZ	rs4765905	PGC SZ[40]	$7{\cdot}0\times10^{-9}$	1·11	*CACNA1C*
BD+SZ	rs4583255	Steinberg et al[41]	$6{\cdot}6\times10^{-11}$	1·08	*MAPK3*
BD+RUD	rs2251219	McMahon et al[42]	$3{\cdot}63\times10^{-8}$	0·87	*PBRM1*

Craddock & Sklar, The Lancet, 2013

Genomic approaches

Genome-wide asscciation studies (GWAS) for the identification of common variants in large samples



Don‘t get fooled into believing it‘s about a couple of genes…we are talking polygenicity here!

GWAS complemented by approaches to identify rare variants

nature Vol 455|11 Septeml

LETTERS

Large recurrent microdeletions associate schizophrenia

Hreinn Stefansson[1]*, Dan Rujescu[2]*, Sven Cichon[3,4]*, Olli P. H. Pietiläinen[5], Andres In
Ragnheidur Fossdal[1], Engilbert Sigurdsson[6], Thordur Sigmundsson[6], Jacobine E. Buizer-
Thomas Hansen[8,9], Klaus D. Jakobsen[8,9], Pierandrea Muglia[10], Clyde Francks[10], Paul M
Arnaldur Gylfason[1], Bjarni V. Halldorsson[1], Daniel Gudbjartsson[1], Thorgeir E.
Adalbjorg Jonasdottir[1], Aslaug Jonasdottir[1], Asgeir Bjornsson[1], Sigurb
Magnus Haraldsson[6], Brynja B. Magnusdottir[6], Ina Giegling[2], H
Kevin V. Shianna[12], Dongliang Ge[12], Anna C. Need[12], C
Jouko Lonnqvist[15], Jaana Suvisaari[15], Annamari
Elvira Bramon[16], Marta Di Forti
Muriel Walshe[16], Tao Li[16,18], C
Srdjan Djurovic[21,22], Ingri
Chiara Sabatti[26], Nelson
Ole A. Andreassen[21,22], R
Hannes Petursson[6], David
Clair[13] & Kari Stefansson[1,

Vol 455|11 September 2008|doi:10.1038/nature07239 nature

TERS

Rare chromosomal d
increase risk of

The Internat

Links to studies in autism, intellectual disability

Cell PRESS

High Frequencies of De Novo CNVs in Bipolar Disorder and Schizophrenia

Dheeraj Malhotra,[1,2,22] Shane McCarthy,[22] Jacob J. Michaelson,[1,2] Vladimir Vacic,[15,22] Katherine E. Burdick,[23] Seungtai Yoon,[5,22] Sven Cichon,[10,11,12] Aiden Corvin,[17] Sydney Gary,[22] Elliot S. Gershon,[21] Michael Gill,[17] Maria Karayiorgou,[18] John R. Kelsoe,[2,4,20] Olga Krastoshevsky,[19] Verena Krause,[19] Ellen Leibenluft,[7] Deborah L. Levy,[19] Vladimir Makarov,[5,22] Abhishek Bhandari,[1,2,22] Anil K. Malhotra,[6] Francis J. McMahon,[14] Markus M. Nöthen,[10,11,16] James B. Potash,[8] Marcella Rietschel,[13] Thomas G. Schulze,[9] and Jonathan Sebat[1,2,3,4,22,*]

Pharmacogenetics

Studies in other fields of medicine that larger effect sizes can be expected for well-defined pharmacoresponse phenotypes.

As always, sample size is critical!

Pharmacogenetics: The *ConLiGen* experience

Neuropsychobiology

Neuropsychobiology 2010;62:72–78
DOI: 10.1159/000314708

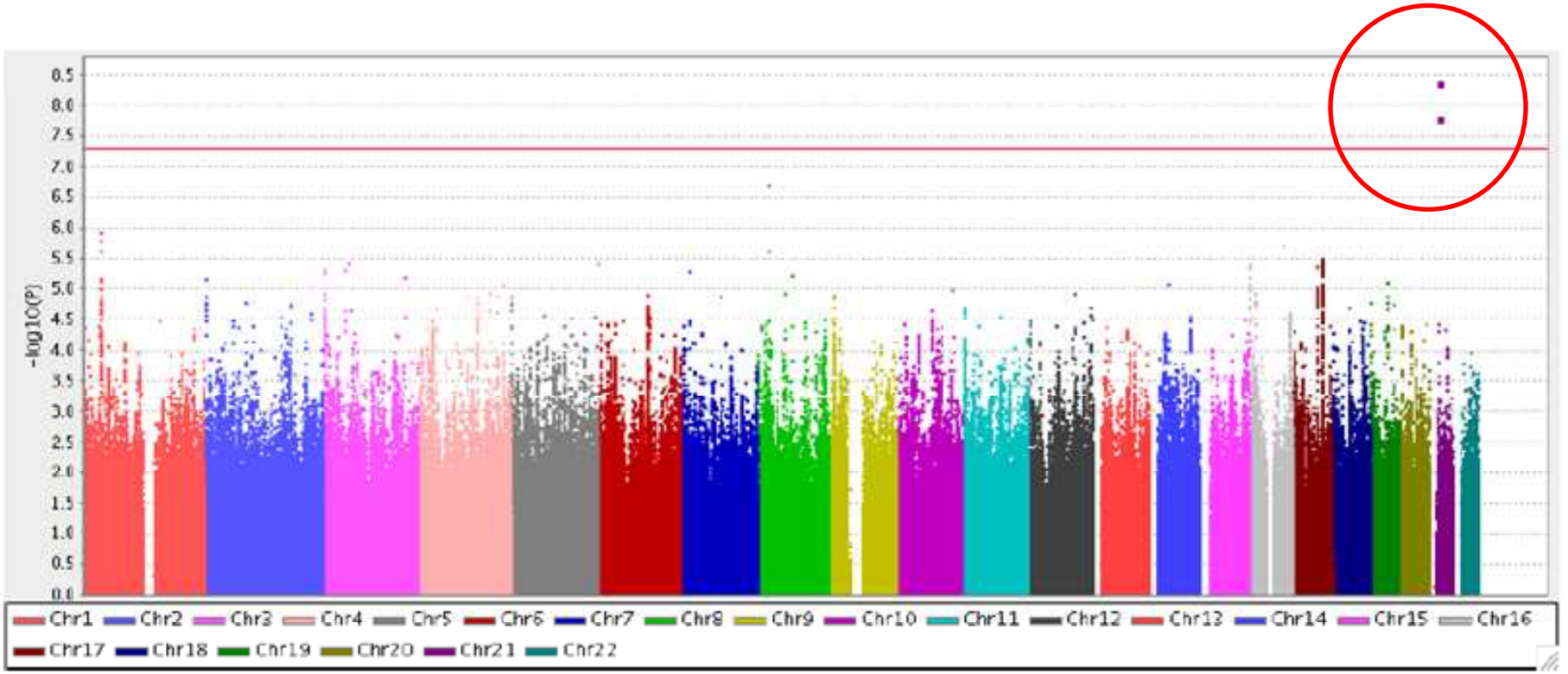
Published online: May 8, 2010

The International Consortium on Lithium Genetics (ConLiGen): An Initiative by the NIMH and IGSLI to Study the Genetic Basis of Response to Lithium Treatment

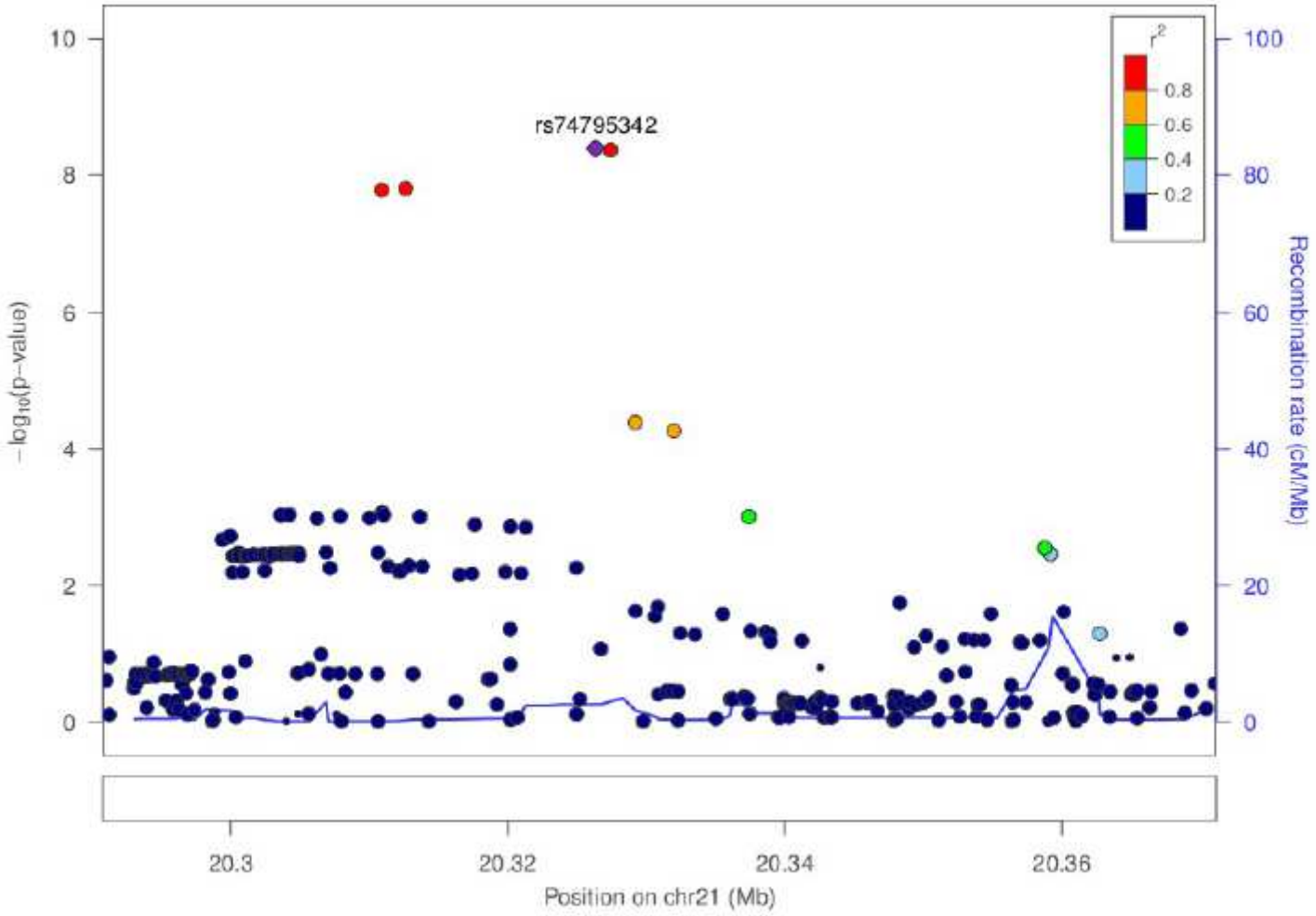
Thomas G. Schulze[a, g, ε] Martin Alda[m, ε] Mazda Adli[h, ε] Nirmala Akula[a]
Raffaella Ardau[t] Elise T. Bui[a] Caterina Chillotti[t] Sven Cichon[i, ζ] Piotr Czerski[v]
Maria Del Zompo[t, u] Sevilla D. Detera-Wadleigh[a] Paul Grof[n, o, ε] Oliver Gruber[j]
Ryota Hashimoto[x, δ] Joanna Hauser[v] Rebecca Hoban[b, c] Nakao Iwata[y, δ] Layla Kassem[a]
Tadafumi Kato[z, δ] Sarah Kittel-Schneider[k] Sebastian Kliwicki[w] John R. Kelsoe[b, c]
Ichiro Kusumi[β, δ] Gonzalo Laje[a] Susan G. Leckband[b, d, e] Mirko Manchia[u] Glenda MacQueen[p]
Takuya Masui[β, δ] Norio Ozaki[γ, δ] Roy H. Perlis[f] Andrea Pfennig[l, ε] Paola Piccardi[u]
Sara Richardson[a] Guy Rouleau[q] Andreas Reif[k] Janusz K. Rybakowski[w, ε] Johanna Sasse[l, ε]
Johannes Schumacher[a, i] Giovanni Severino[u] Jordan W. Smoller[f] Alessio Squassina[u]
Gustavo Turecki[r] L. Trevor Young[s, ε] Takeo Yoshikawa[α, δ] Michael Bauer[l, ε]
Francis J. McMahon[a]

Pharmacogenetics: The *ConLiGen* experience

Pharmacogenetics: The *ConLiGen* GWAS



Pharmacogenetics: The *ConLiGen* GWAS



Pharmacogenetics: The *ConLiGen* GWAS

- Our finding is genome-wide significant
- rs74795342 and rs75222709 lie in the intronic region of the *AL157359.3* gene
- rs79663003 and rs78015114 lie13-15 kb downstream
- AL157359.3 codes for a “long noncoding RNA” (lncRNA)
- lncRNA transcripts are longer than 200 nucleotides
- Involved in a multitude of cell regulatory processes

Subphenotype approaches

e.g. delusional content

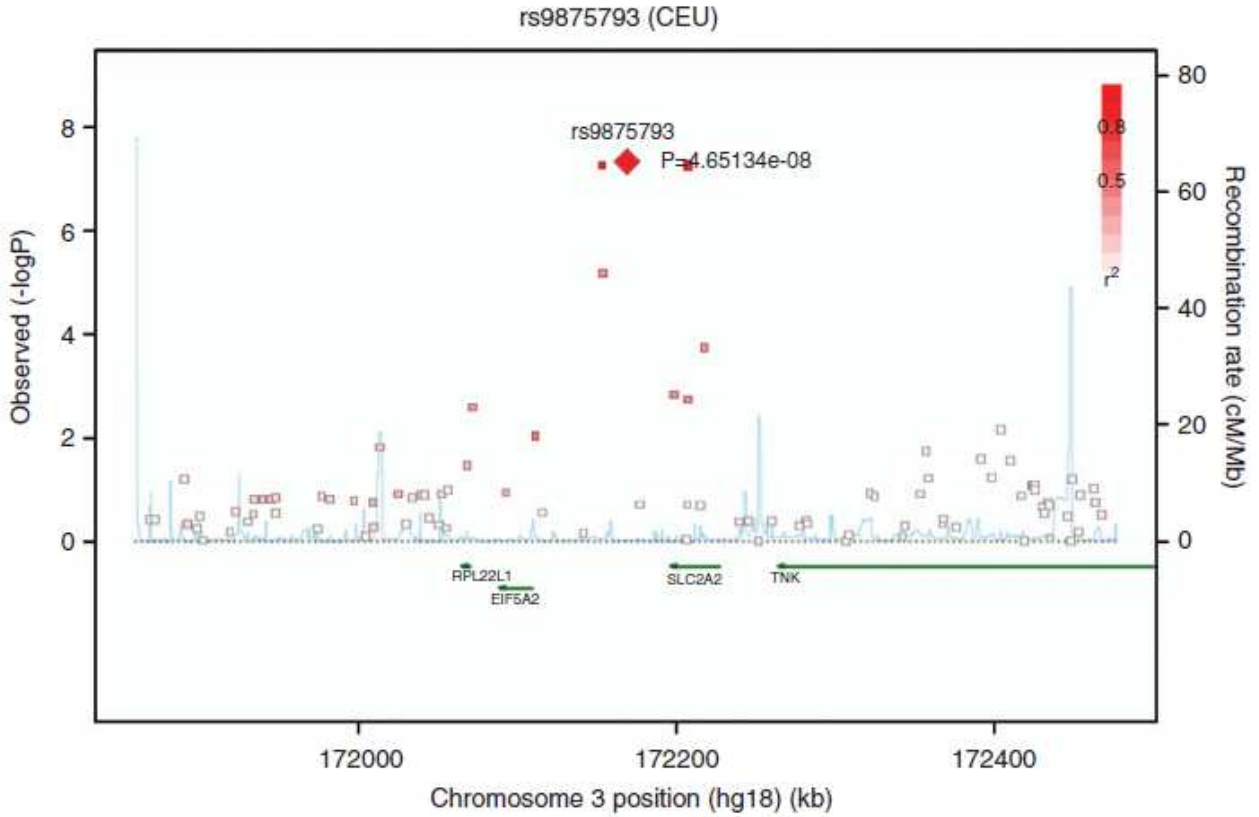
Citation: Transl Psychiatry (2012) 2, e165; doi:10.1038/tp.2012.81

www.nature.com/tp

Genome-wide significant association between a 'negative mood delusions' dimension in bipolar disorder and genetic variation on chromosome 3q26.1

S Meier[1], M Mattheisen[2,3,4], E Vassos[5], ,
B Müller-Myhsok[7], M Steffens[8], C Schma
S Cichon[2,6,11], TG Schulze[12,14] and M R

Research suggests that clinical sympt
than standard diagnostic models. To c
(GWAS). We performed a GWAS of fa
Rs9875793, which is located in an inter
transporter), member 2 gene (*SLC2A2*),
delusions' ($n = 927$; $P = 4.65 \times 10^{-8}$,
poverty, delusions of guilt and nihilis
rs9875793 was only observed in the su
model: $P_G = 0.0001$, OR = 1.92; item pr
patients displaying 'negative mood del
sample (GAIN/TGEN), which included 1
Translational Psychiatry (2012) 2, e165; d



Subphenotype approaches

e.g. attempted suicide

Molecular Psychiatry (2011), 1–12

www.nature.com/mp

ORIGINAL ARTICLE

A genome-wide association study of attempted suicide

VL Willour[1], F Seifuddin[1], PB Mahon[1], D Jancic[1], M Pirooznia[1], J Steele[2], B Schweizer[1], FS Goes[1], FM Mondimore[1], DF MacKinnon[1], The Bipolar Genome Study (BiGS) Consortium, RH Perlis[3], PH Lee[3], J Huang[3], JR Kelsoe[4], PD Shilling[4], M Rietschel[5,6], M Nöthen[7], S Cichon[8,9], H Gurling[10], S Purcell[3], JW Smoller[3], N Craddock[11], JR DePaulo Jr[1], TG Schulze[2,12], FJ McMahon[2], PP Zandi[1] and JB Potash[1]

Chromosome Region	Best SNP in Region	RefSeq[1] Gene	RefSeq Genes in LD	Initial Odds Ratio[2]	Initial P-value	Replication Odds Ratio[2]	Replication P-value	Combined P-value
2p25	rs300774	Intergenic	*SH3YL1, ACP1, FAM150B*	1.42	$1.09X\ 10^{-6}$	1.22	0.0036	$5.07\ X\ 10^{-8}$
11p13	rs10437629	*C11orf41*	None	1.62	$8.56\ X\ 10^{-5}$	1.34	0.0078	$3.77\ X\ 10^{-6}$
12q24	rs7296262	*TMEM132C*	None	1.43	$9.08\ X\ 10^{-6}$	1.22	0.011	$1.09\ X\ 10^{-6}$

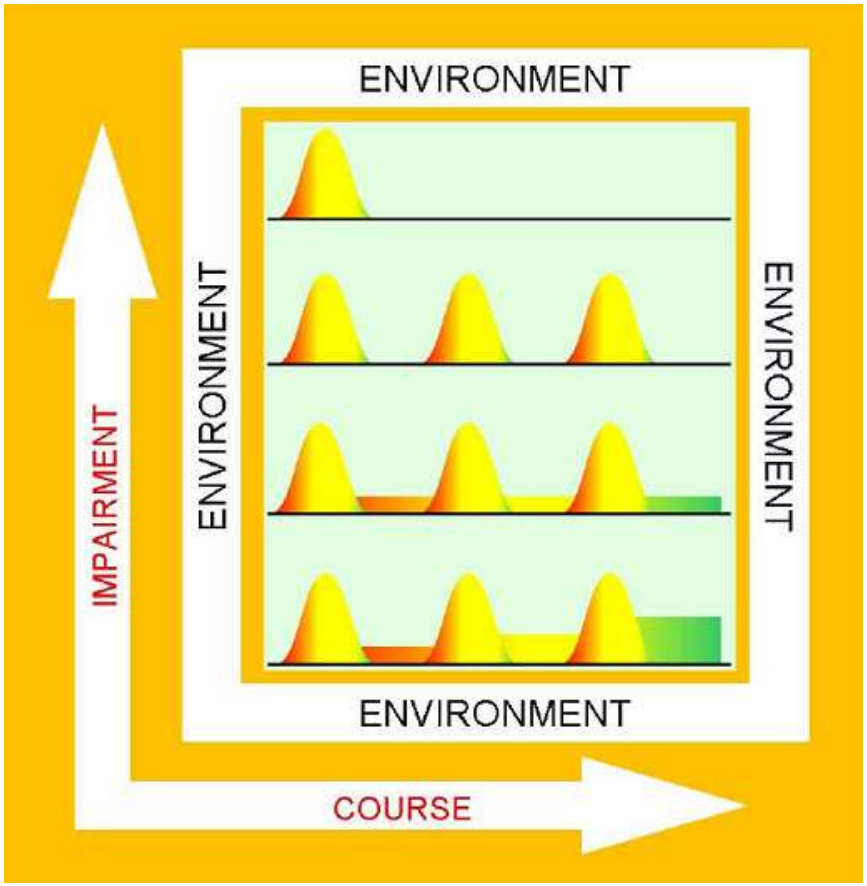
Where would we like to be in 2025?

A wish list

1. A large set of validated risk genes for disease phenotypes (categorical, dimensional)
2. A large set of validated genes for personalized medicine approaches (pharmacogenetics)
3. Bidirectional translation: human model ←→ systems biology
4. Genetics as a tool to better understand all the above across life trajectories
5. Clinical applicability: predictive and prognostic use of genetics

How can we get there? Think trajectories!

Trajectorial thinking



- has gained some traction in biological psychiatry
- however, it‘s in its infancy at its best as most studies are still cross-sectional
- is still hampered by an (artificial) divide between adult and child & adolescent psychiatry
- is needed in order to develop clinical applicability: predictive and prognostic use of genetics

Mental illness doesn’t suddenly develop at age18

SCIENCE sciencemag.org 31 OCTOBER 2014 • VOL 346 ISSUE 6209 547

MENTAL HEALTH

Adolescent mental health–Opportunity and obligation

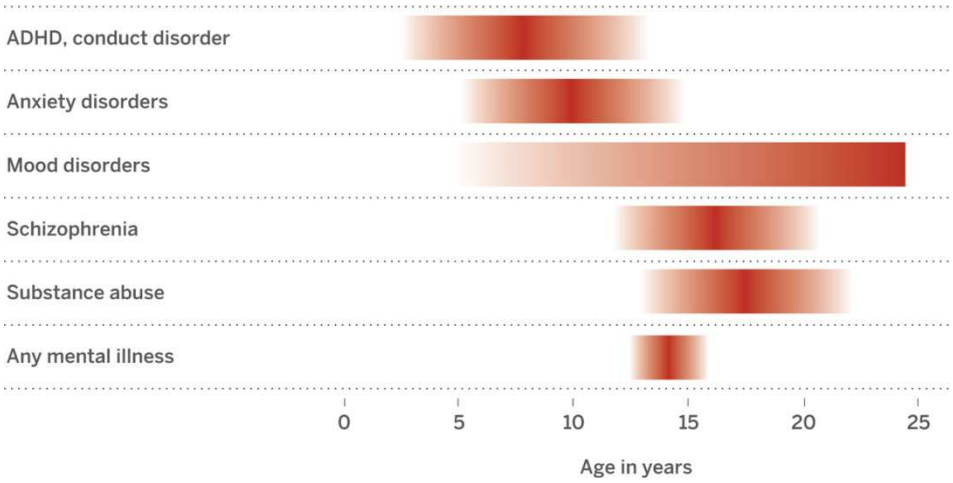
Emerging neuroscience offers hope for treatments

By Francis S. Lee,[1] Hakon Heimer,[2,3] Jay N. Giedd,[4] Edward S Lein,[5] Nenad Šestan,[6] Daniel R. Weinberger,[7,8] B. J. Casey[1]*

of mental disorders and how they affect treatment efficacy is imperative. Yet, we estimate that less than 1% of the budget of the U.S. National Institutes of Health (NIH)

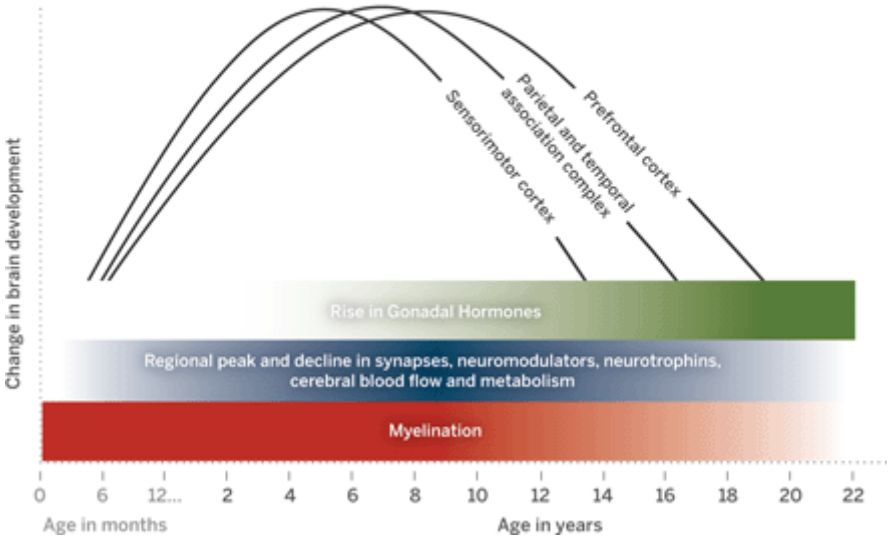
Emergence and peak in mental disorders during adolescence

One in five adolescents have a mental illness that will persist into adulthood

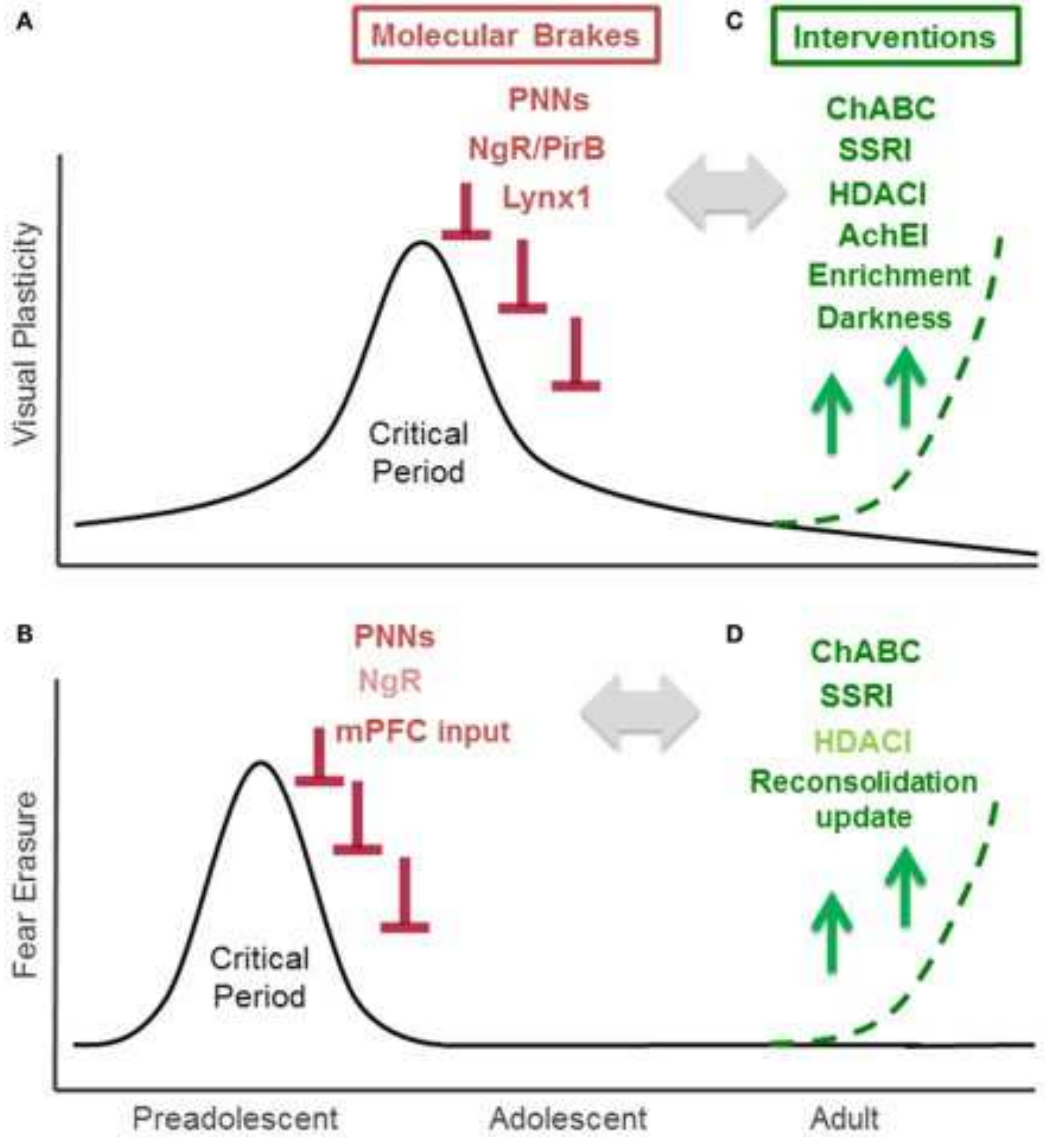


Developmental course of brain maturation during adolescence

Behavioral attributes are paralleled by hormonal and neurobiological changes that target specific brain regions and cell populations



Mental illness doesn't suddenly develop at age18



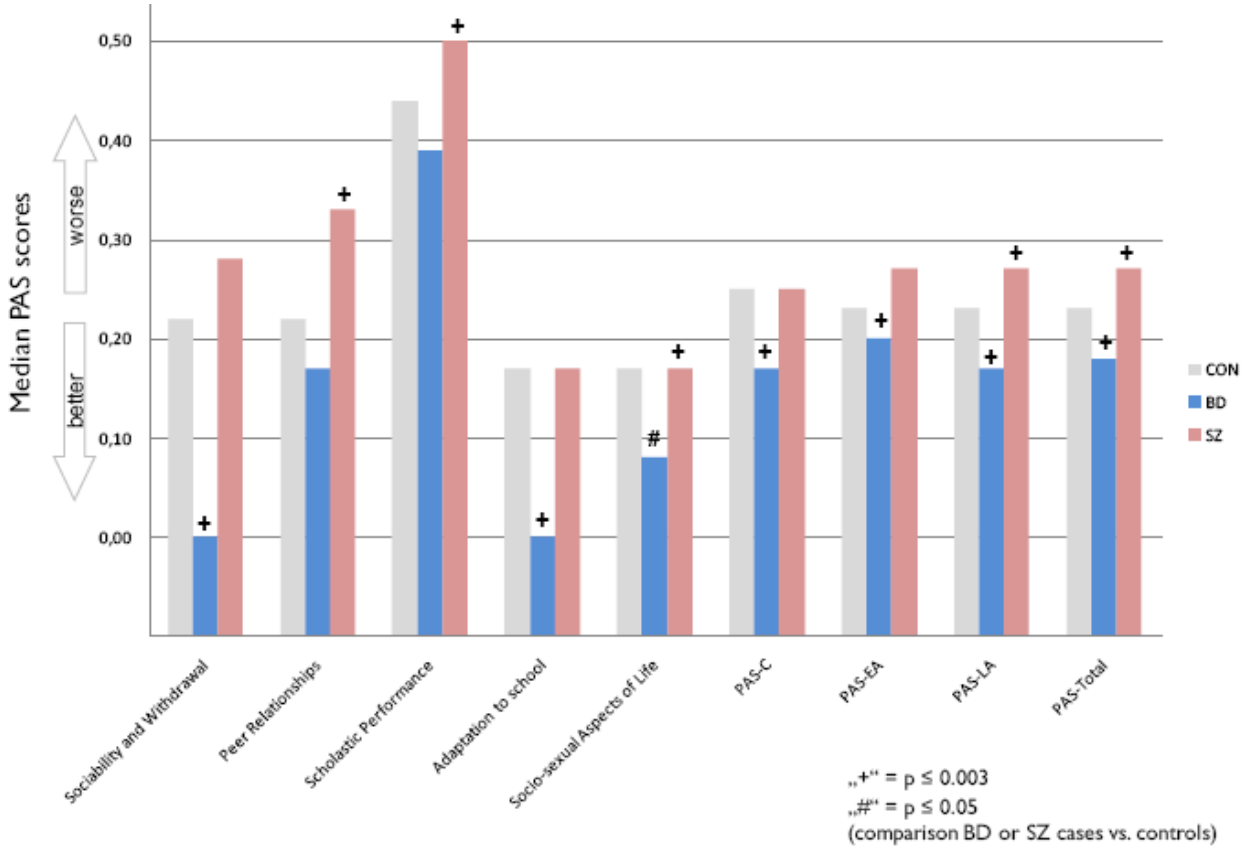
Nabel & Morishita, *Frontiers in Psychiatry*, 2013

Premorbid aspects

Premorbid adjustment: A phenotype highlighting a distinction rather than an overlap between schizophrenia and bipolar disorder ☆,☆☆

Marcella Rietschel [a], Alexander Georgi [a], Christine Schmael [a], Frederike Schirmbeck [a], Jana Strohmaier [a], Katja V. Boesshenz [a], Markus Schwarz [b], Markus M. Nöthen [c], Thomas G. Schulze [a,*]

Schizophrenia Research 110 (2009) 33–39



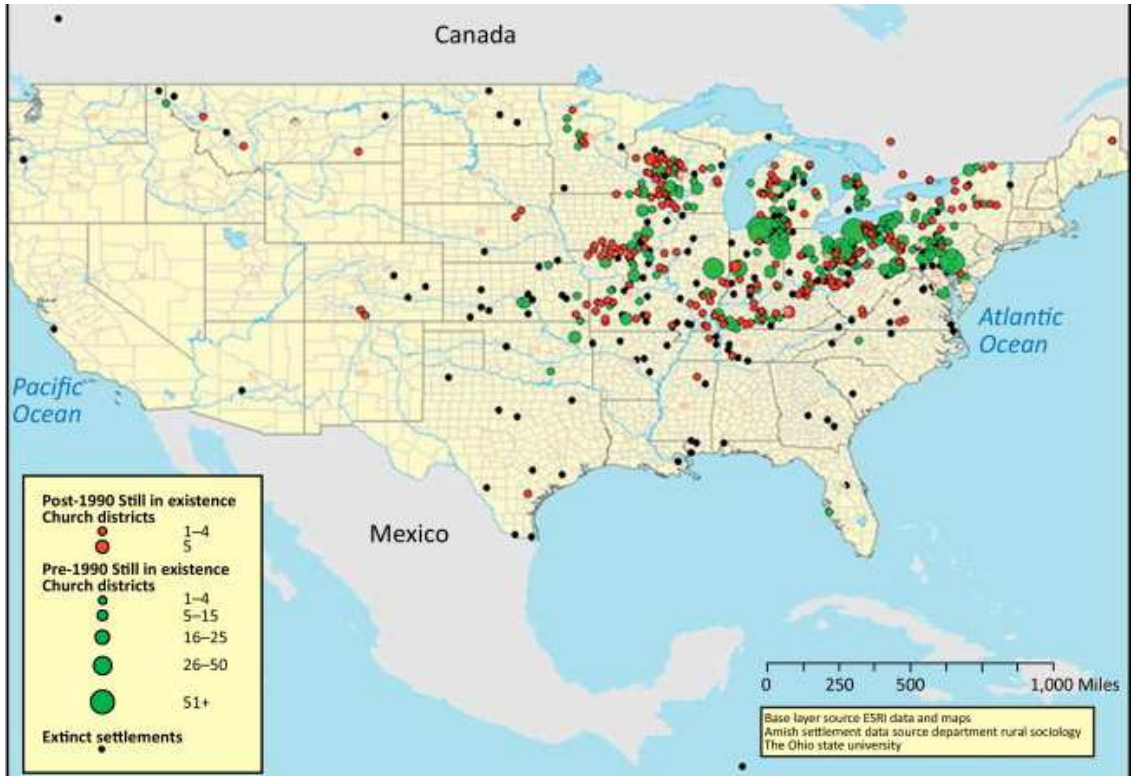
A case in point: genomic studies in the Amish

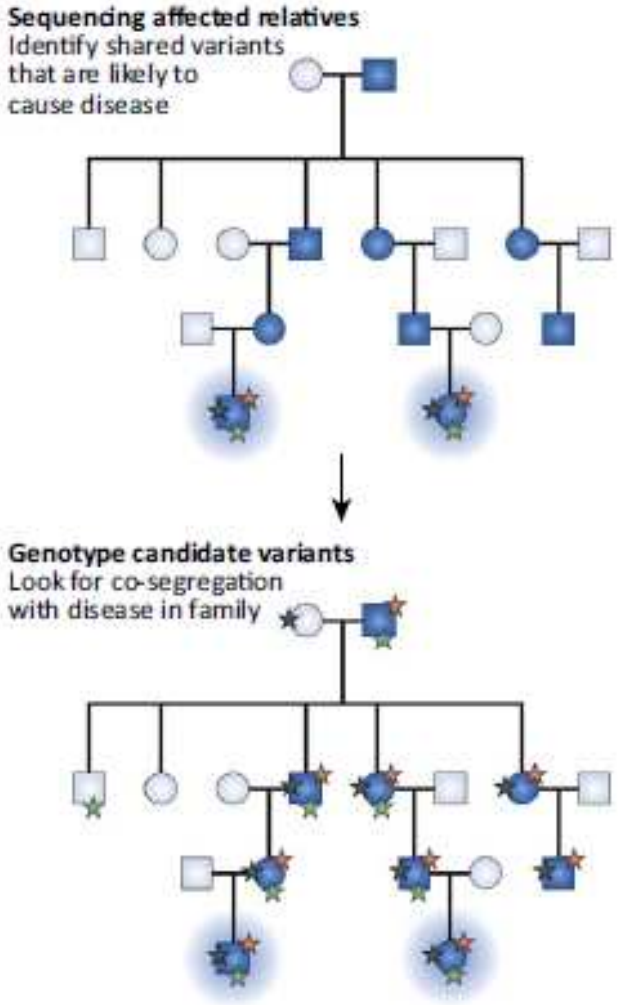
Review

Trends in Genetics, Feb 16, 2013

Amish revisited: next-generation sequencing studies of psychiatric disorders among the Plain people

Liping Hou[1], Gloria Faraci[1], David T.W. Chen[1], Layla Kassem[1], Thomas G. Schulze[2], Yin Yao Shugart[3], and Francis J. McMahon[1]

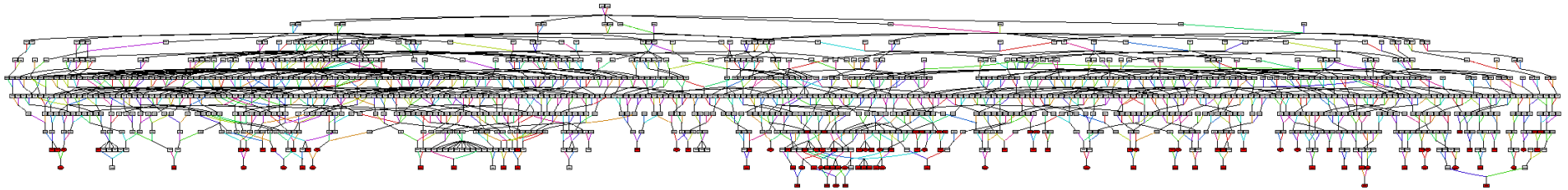


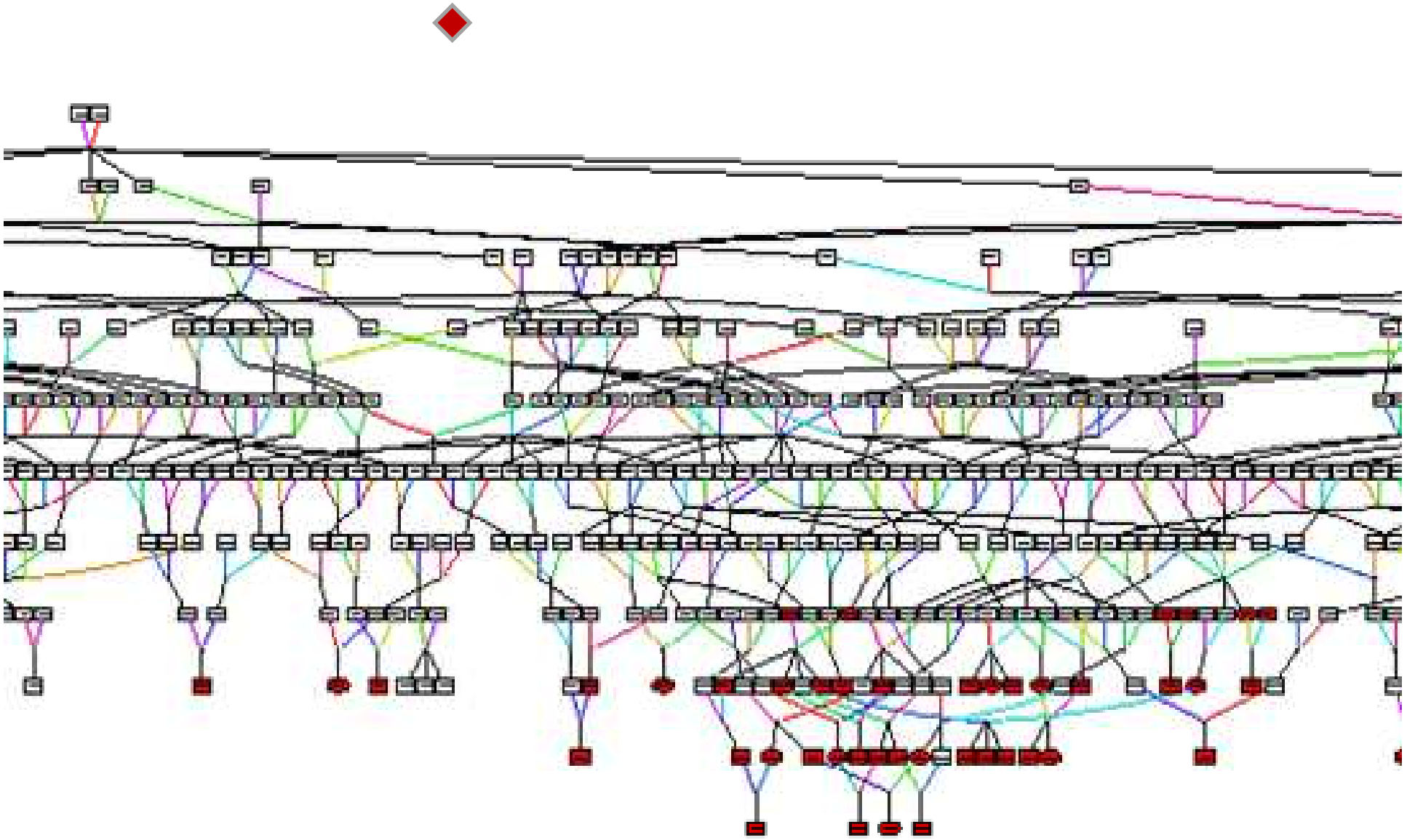


A case in point: genomic studies in the Amish

A case in point: genomic studies in the Amish

Amish study: most individuals belong to one large pedigree!





Joining forces

The power of genomics & comprehensive phenotyping in children at risk

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Short communication

An fMRI study of emotional face encoding in youth at risk for bipolar disorder

W.-L. Tseng [a,*], B.L. Bones [b], R.R. Kayser [b], A.K. Olsavsky [c], S.J. Fromm [a], D.S. Pine [a], E. Leibenluft [a], M.A. Brotman [a]

The infrastructure needed for trajectorial approaches

Molecular Psychiatry (2012), 1–6

www.nature.com/mp

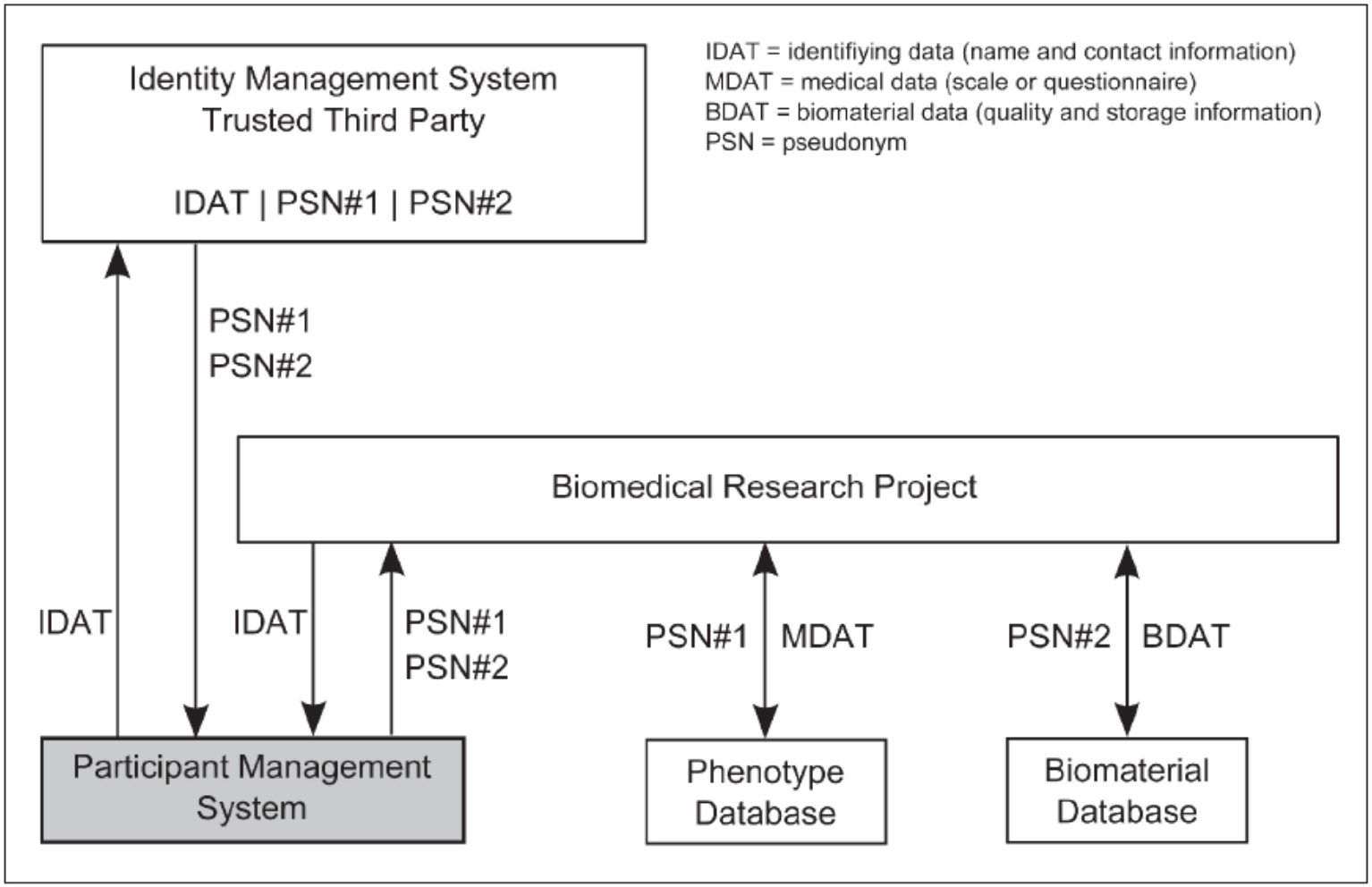
PERSPECTIVE

Managing sensitive phenotypic data and biomaterial in large-scale collaborative psychiatric genetic research projects: practical considerations

SY Demiroglu[1], D Skrowny[1], M Quade[1], J Schwanke[1], M Budde[2], V Gullatz[2], D Reich-Erkelenz[2], JJ Jakob[1], P Falkai[2,3], O Rienhoff[1], K Helbing[1], U Heilbronner[2] and TG Schulze[2]

[1]*Department of Medical Informatics, University Medical Center Göttingen, Göttingen, Germany,* [2]*Section on Psychiatric Genetics, Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, Germany and* [3]*Department of Psychiatry and Psychotherapy, Ludwigs-Maximilians-University, München, Germany*

The infrastructure needed for trajectorial approaches



Schwanke J et al., Methods Inf Med, 2013

The infrastructure needed for trajectorial approaches

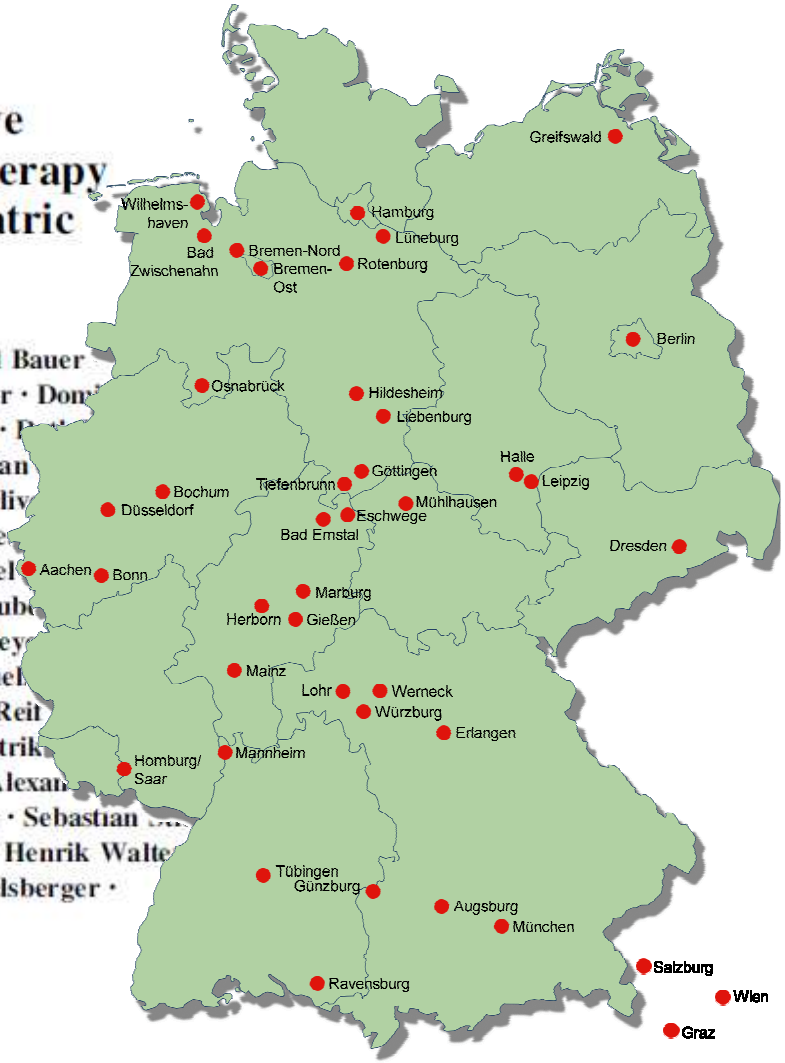
Eur Arch Psychiatry Clin Neurosci
DOI 10.1007/s00406-013-0401-8

SHORT COMMUNICATION

The "DGPPN-Cohort": a national collaboration initiative by the German Association for Psychiatry and Psychotherapy (DGPPN) for establishing a large-scale cohort of psychiatric patients

Heike Anderson-Schmidt · Lothar Adler · Chadiga Aly · Ion-George Anghelescu · Michael Bauer · Jessica Baumgärtner · Joachim Becker · Roswitha Bianco · Thomas Becker · Cosima Bitter · Karoline Buckow · Monika Budde · Michael Dümpelmann · Uta Engelh · Here Folkerts · Michael Franz · Ka · Verena Gullatz · Linda Gusky · Ur · Tilman Hensch · Christoph Hiemke · Wolfgang P. Kaschka · Tilo Kirche · Axel Krug · Mahsa Lee · Markus L · Moritz Mühlbacher · Matthias J. Müller · Vanessa Nieratschker · Barbara Nierste · Jacquel · Andrea Pfennig · Marlenna Pieper · Matthias Quade · Daniela Reich-Erkelenz · Andreas Reit · Bernd Reininghaus · Eva Z. Reininghaus · Matthias Riemenschneider · Otto Rienhoff · Patrik · Dan Rujescu · Rebecca Schennach · Harald Scherk · Max Schmauss · Frank Schneider · Alexan · Björn H. Schott · Sybille G. Schwab · Jens Schwanke · Daniela Skrowny · Carsten Spitzer · Sebastian · Judith Stöckel · Susanne Stübner · Andreas Thiel · Hans-Peter Volz · Martin von Hagen · Henrik Walte · Stephanie H. Witt · Thomas Wobrock · Jürgen Zielasek · Jörg Zimmermann · Antje Zitzelsberger · Wolfgang Maier · Peter G. Falkai · Marcella Rietschel · Thomas G. Schulze

DGPPN
Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde



Concluding remarks

- We did not get what we hoped for three decades ago, i.e. a handful of major risk genes (oligogenic model)
- But still, psychiatric genetics has made tremendous progress over the last decade
- Over 100 genes identified for schizophrenia
- Similar developments expected for other disorders as sample sizes increase and subphenotype approaches are being applied
- Clear evidence for polygenicity

- There are many findings awaiting further vetting
- Out-of-the-box follow-up studies are warranted
- Most importantly, we have to think in trajectories: to better understand the continuity of psychopathology, genetic studies have to start before age 18!
- In particular, as genetic testing has already become a reality

The reality of genetic testing today

1. Commercial panels marketed to psychiatrists and psychologists
   - Recurrent CNVs associated with developmen
   - Cytochrome p450 markers
   - SERT LPR
2. Direct m ts and their relatives

We cannot cede this field to commercial interest alone

for autism by private companies		
	Location	Tests offered
	Gaithersburg, Maryland	CNV microarray; selective gene sequencing
Athena Diagnostics	Worcester, Massachusetts	CNV microarray; selective gene sequencing
Ambry Genetics	Aliso Viejo, California	CNV microarray; selective gene sequencing
Lineagen	Salt Lake City, Utah	CNV microarray; selective gene sequencing
Signature Genomics	Spokane, Washington	CNV microarray
Combimatrix	Irvine, California	CNV microarray
Population Diagnostics*	Long Island, New York	CNV screening
IntegraGen*	Cambridge, Massachusetts	SNP panel

*test under development

Waters, *Nat Medicine* 2011


ISPG
Home
About Us
Membership
Annual World Congress
Resources
Job Postings
Member Login
Genetic testing statement by the ISPG
INTERNATIONAL SOCIETY OF
PSYCHIATRIC GENETICS

Thanks to

Klinik für Psychiatrie, LMU, München
Peter Falkai

Abteilung für Medizininformatik, UMG, Göttingen
Linda Gusky
Krister Helbing
Sara Nußbeck
Otto Rienhoff
Jens Schwanke
Daniela Skrowny
Matthias Quade

Inst. für Humangenetik, Universität Bonn
Sven Cichon
Markus M. Nöthen

ZI, Mannheim
Marcella Rietschel
Jana Strohmaier

Human Genetics Branch NIMH, Bethesda, MD, USA
Nirmala Akula
Sevilla Detera-Wadleigh
Liping Hou
Francis J. McMahon

Dept. of Psychiatry, The Johns Hopkins University, Baltimore, MD, USA
J. Ray DePaulo
James B. Potash
Peter F. Zandi

DFG Deutsche Forschungsgemeinschaft

NGFN Nationales Genomforschungsnetz

NARSAD The World's Leading Charity Dedicated to Mental Health Research

NIMH National Institute of Mental Health