NATIONAL ACADEMIES OF SCIENCES, ENGINEERING, MEDICINE

Washington, September 12th, 2016

Selective disease model development in Schizophrenia

Niels Plath, PhD, VP for Synaptic Transmission, Lundbeck

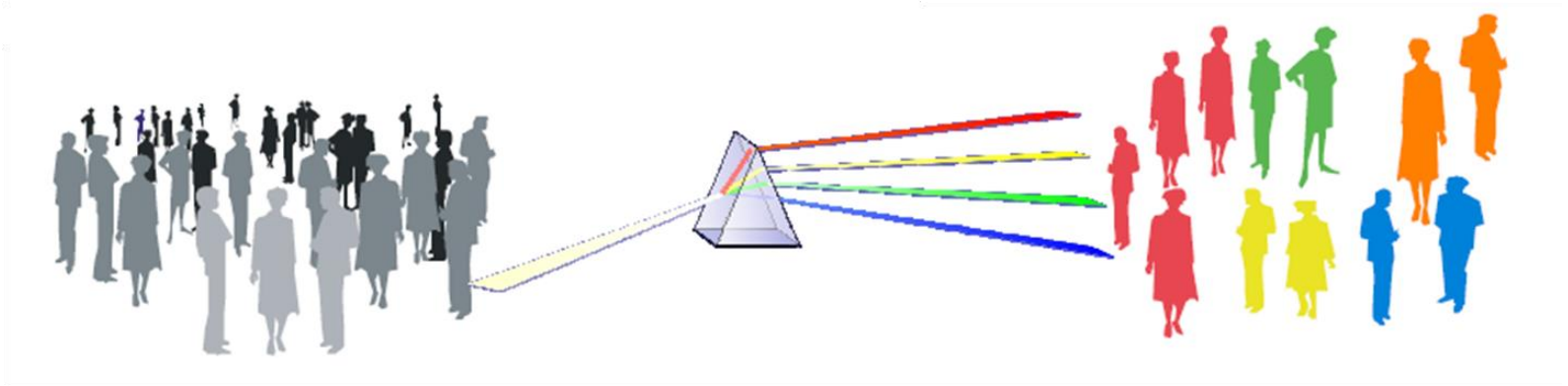
Lundbeck

Modelling schizophrenia – but what?

"One of the difficulties in defining schizophrenia is the possibility of its heterogeneity"

Ming T Tsuang (Biol Psychiatry, **1975**)

Phenotypic heterogeneity ? **Etiologic heterogeneity**



There will never be one "animal model of Schizophrenia", but…

… we have progressed our understanding of heterogeneity

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

LETTERS

Rare chromosomal deletions and duplications increase risk of schizophrenia

The International Schizophrenia Consortium*

Schizophrenia is a severe mental disorder marked by hallucinations, delusions, cognitive deficits and apathy, with a heritability estimated at 73–90% (ref. 1). Inheritance patterns are complex, and the number and type of genetic variants involved are not understood. Copy number variants (CNVs) have been identified in individual patients with schizophrenia[2–7] and also in neurodevelopmental disorders[8–11], but large-scale genome-wide surveys have not been performed. Here we report a genome-wide survey of rare CNVs in 3,391 patients with schizophrenia and 3,181 ancestrally mat… rays. For CNVs that … and were more than … increased 1.15-fold i… with controls. This …le-occurrence CN… posed to those that … within the region crit… includes psychotic … ons with schizophre… omosome 15q13.3 an… usly been reported, … wide correction. O… of schizophrenia … structural variants, both genome-wide and at specific loci.

22q11.21
1q21.1
15q13.3

Informati… 182.1 kb (… deletions … the impac… two ways: … second by … with disea…

Structu… mental di… phrenia n… posited a … loci have … neurodev… extent to … phrenia ir… atypical … retardatio… with schi… Consideri… burden th… for array … person, w… We ne… observati…

LETTERS

Strong association of *de novo* … with sporadic schizophrenia

Bin Xu[1,2], J Louw Roos[3], Shawn Levy[4], E J van Rensburg…

Schizophrenia is an etiologically heterogeneous psychiatric disease, which exists in familial and nonfamilial (sporadic) forms[1]. Here, we examine the possibility that rare *de novo* copy number (CN) mutations with relatively high penetrance contribute to the genetic component of schizophrenia. We carried out a whole-genome scan and implemented a number of steps for finding and confirming CN mutations. Confirmed *de novo* mutations were significantly associated with schizoph… ~8 times more fr… ith schizoph… rison, rare inf… riched in sporadi… germline mutations contribute to schizophrenia vulnerability in sporadic cases and that rare genetic lesions at many different loci can account, at least in part, for the genetic heterogeneity of this disease.

22q11.21

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.

LETTERS

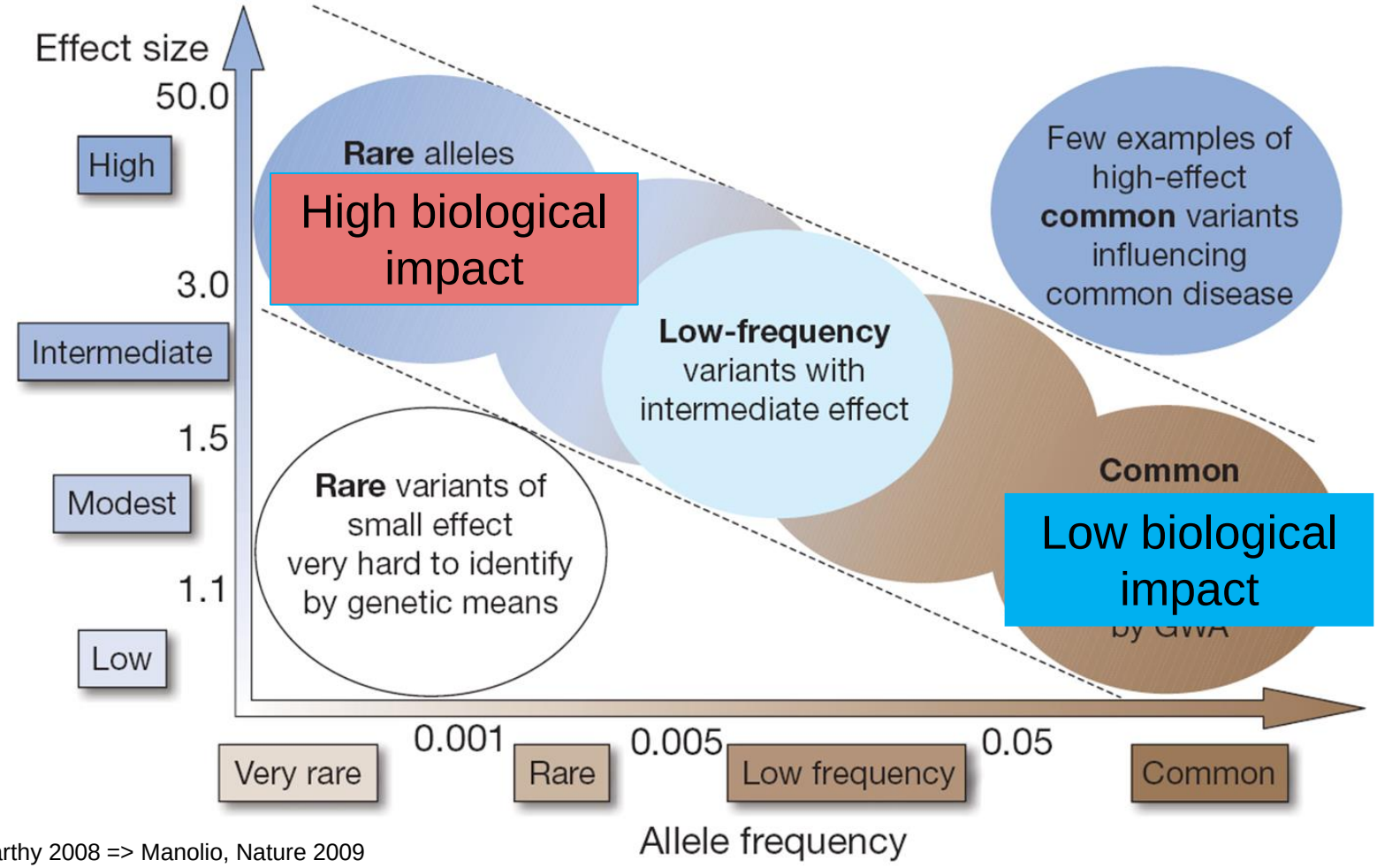
Large recurrent microdeletions associated with schizophrenia

Hreinn Stefansson[1]*, Dan Rujescu[2]*, Sven Cichon[3,4]*, Olli P. H. Pietiläinen[5], Andres Ingason[1], Stacy Steinberg[1], Ragnheidur Fossdal[1], Engilbert Sigurdsson[6], Thordur Sigmundsson[6], Jacobine E. Buizer-Voskamp[7], Thomas Hansen[8,9], Klaus D. Jakobsen[8,9], Pierandrea Muglia[10], Clyde Francks[10], Paul M. Matthews[11], Ari… n[1], Daniel Gudbjartsson[1], Thorgeir E. Thorgeirsson[1], Asgeir Sigurdsson[1], Ad… tir[1], Asgeir Bjornsson[1], Sigurborg Mattiasdottir[1], Thorarinn Blondal[1], Ma… lottir[6], Ina Giegling[2], Hans-Jürgen Möller[2], Annette Hartmann[2], Ke… a C. Need[12], Caroline Crombie[13], Gillian Fraser[13], Nicholas Walker[14], Jou… namarie Tuulio-Henriksson[15], Tiina Paunio[5,15], Timi Toulopoulou[16], Ely… Murray[16], Mirella Ruggeri[17], Evangelos Vassos[16], Sarah Tosato[17], Mu… silescu[3], Thomas W. Mühleisen[3], August G. Wang[19], Henrik Ullum[20], Src… lesen[23], Lambertus A. Kiemeney[24], Barbara Franke[25], GROUP†, Ch… frey R. Gulcher[1], Unnur Thorsteinsdottir[1], Augustine Kong[1], Ol… [27], Alexander Georgi[28], Marcella Rietschel[28], Thomas Werge[8], Ha… , Markus M. Nöthen[3,4], Leena Peltonen[5,29,30], David A. Collier[16,18], David St Clair[13] & Kari Stefansson[1,31]

1q21.1
15q11.2
15q13.3

Lundbeck

Common variants vs. rare variants



From McCarthy 2008 => Manolio, Nature 2009

Generating animal models of genetic risk factors

Table 1. Genomic regions implicated by rare structural variants in schizophrenia[a]

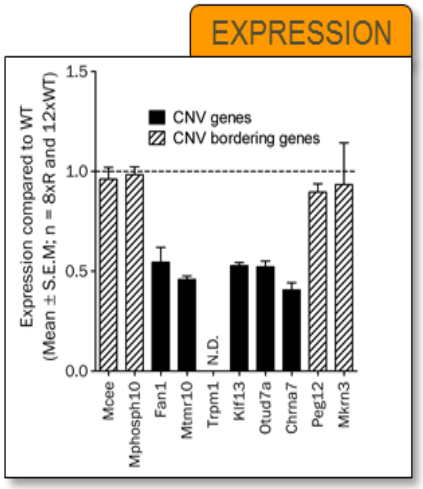
Locus[b]	Gene(s)[c,d]	Copy number change	Frequency in SCZ (%)	OR	Reference	Other Associated Disorders[d]
Replicated significant associations from case-control studies[e]						
1q21.1	~10 genes	Deletion	0.23-0.32	6.6-14.8	[12,13]	DD,CM [60,70]
15q13.3	~10 genes	Deletion	0.17-0.3	11.5-17.9	[12,13]	GE [71,72], MR [73]
16p11.2	>25 genes	Duplication	0.3	8.3-25.4	[11,53]	ASD, BD, MD, P-NOS [53,62]
22q11.2	>25 genes	Deletion	0.5-2.0	30	[12,13,37]	VCFS [42], Anxiety, Depression, ADHD, OCD [69]

[a]Abbreviations: ASD, autism spectrum disorder; DD, developmental delay; CM, congenital malformations; GE, generalized epilepsy; MR, mental retardation; BD, bipolar disorder; P-NOS, psychosis not otherwise specified; VCFS, Velocardiofacial syndrome; ADHD, attention-deficit hyperactivity disorder; OCD, obsessive compulsive disorder; HNPP. hereditary neuropathy with liability to pressure palsies; MD, major depressive disorder.

Sebat J. et al, 2009

Human 15q13.3	Mouse 7qC
	Mcee
	Mphosph10
Mtmr15 (Fan1)	**Mtmr15 (Fan1)**
Mtmr10	Mtmr10
Trpm1	Trpm1
Mir211	Mir211
Klf13	Klf13
Otud7a	Otud7a
Chrna7	**Chrna7**
	Peg12
	Mkrn3

(Df[h15q13]/+) mouse

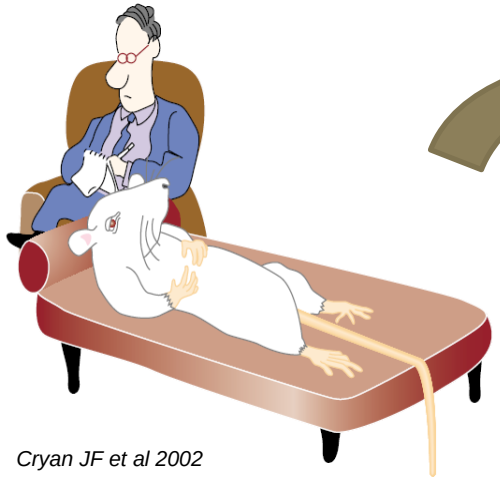


Fejgin et al., 2014

15q13 hemizygousity as a construct model for CNV mediated Schizophrenia

Closing in on the “translational gap”

Phenotypic heterogeneity



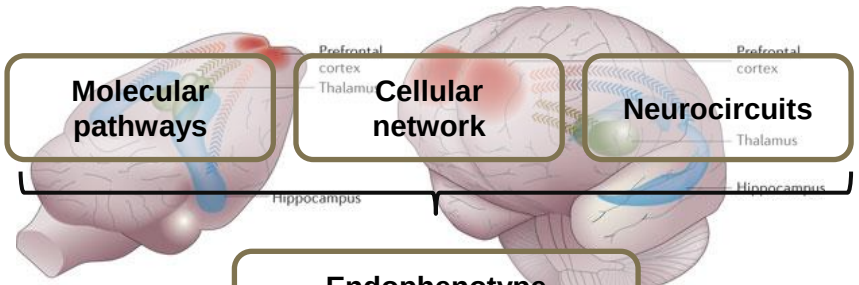
Cryan JF et al 2002

?

Molecular pathways

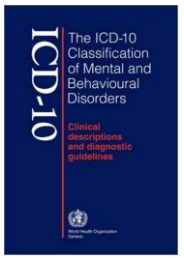
Cellular network

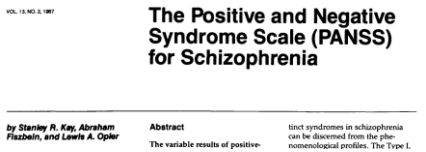
Neurocircuits



Endophenotype
Intermediate phenotype

?





The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia

by Stanley R. Kay, Abraham Fiszbein, and Lewis A. Opler

Abstract

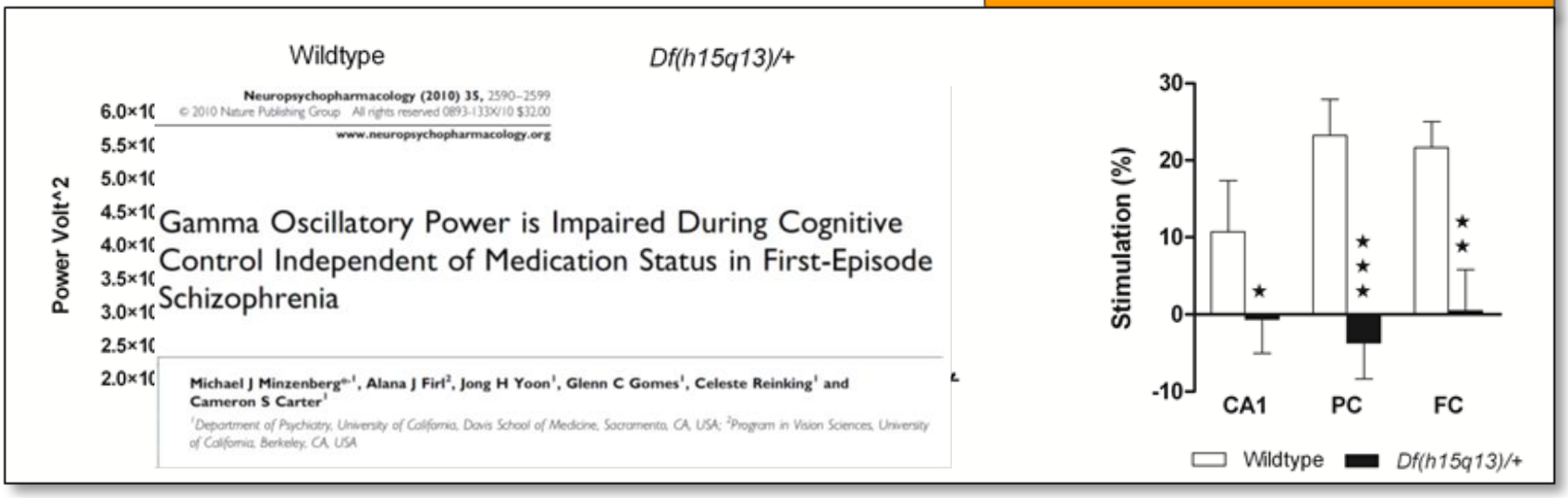
The variable results of positive-

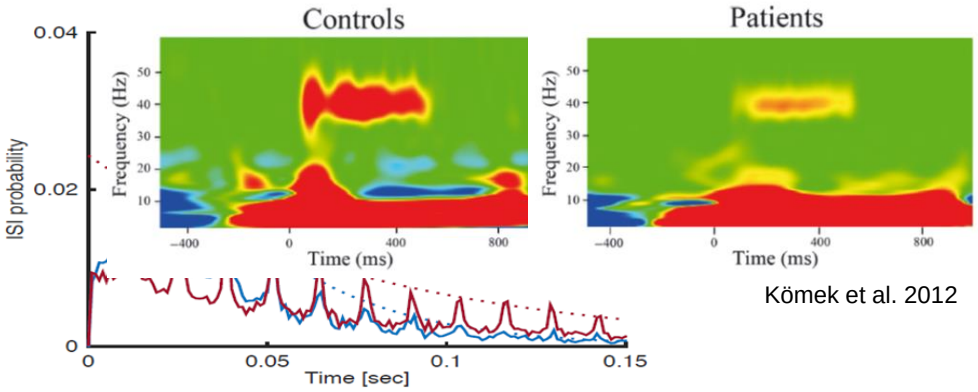
tinct syndromes in schizophrenia can be discerned from the phenomenological profiles. The Type I.

Identifying endophenotypes in the 15q13.3 mouse model

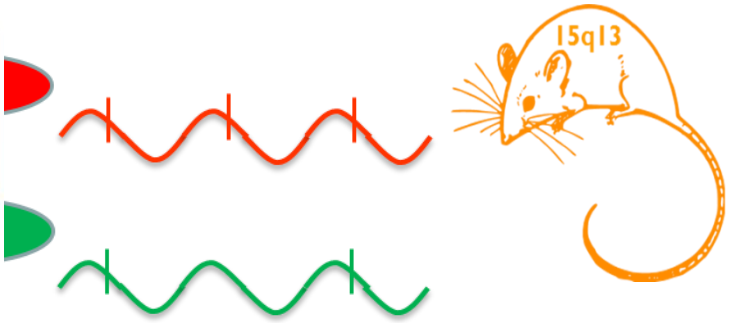
15q13 mice show strong impairment in gamma oscillations when paced at 40 Hz with auditory stimuli

GAMMA OSCILLATIONS





Kömek et al. 2012



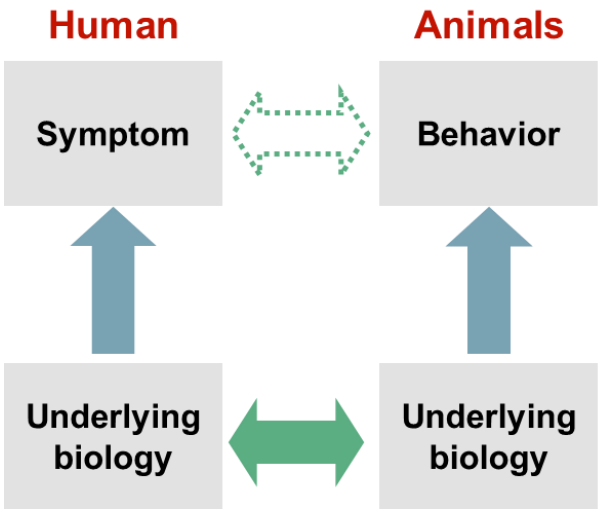
FSI = fast spiking interneurons

Fejgin K et al., 2014
Thelin J et al., 2016
Gass N et al., 2016
Nilsson S et al., 2016

Summary

Risk factor → Endophenotype → Symptom → Function ?

- **Opportunities**
  - Endophenotypes identified via risk factors that model a specific patient subgroup
  - Translational validity of endophenotypes that allows for biomarker development
  - Markers that might lead to earlier and more precise diagnoses
  - This represents a tool for novel target identification



- **Challenges ahead**
  - Linking endophenotypes to clinical symptoms and functional outcome
  - Extrapolation of rare genetics derived endophenotypes to broader patient populations

- This requires common and coordinated research efforts, also between academia and industry, as well as integrated pre-clinical and exploratory clinical studies

Outlook:
Target identification based on risk factor models