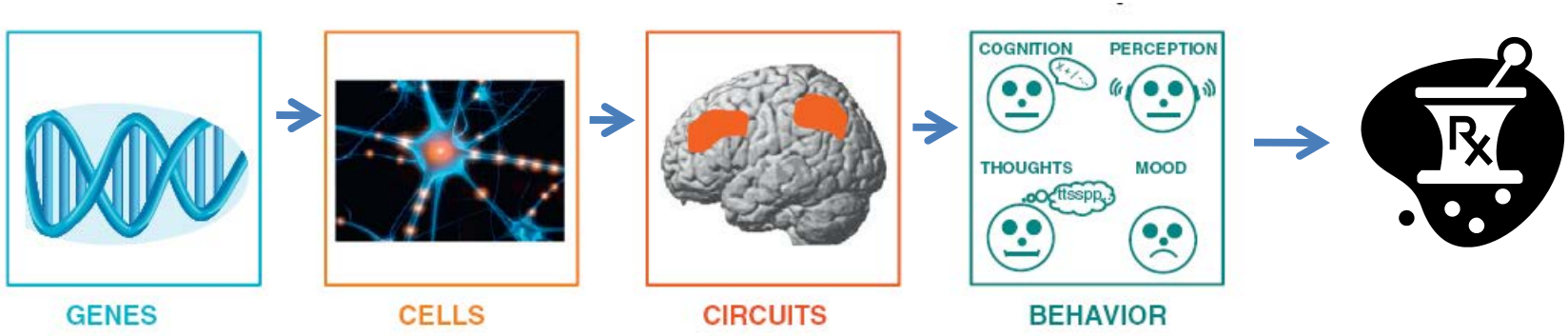
From genes to brain to new therapeutics



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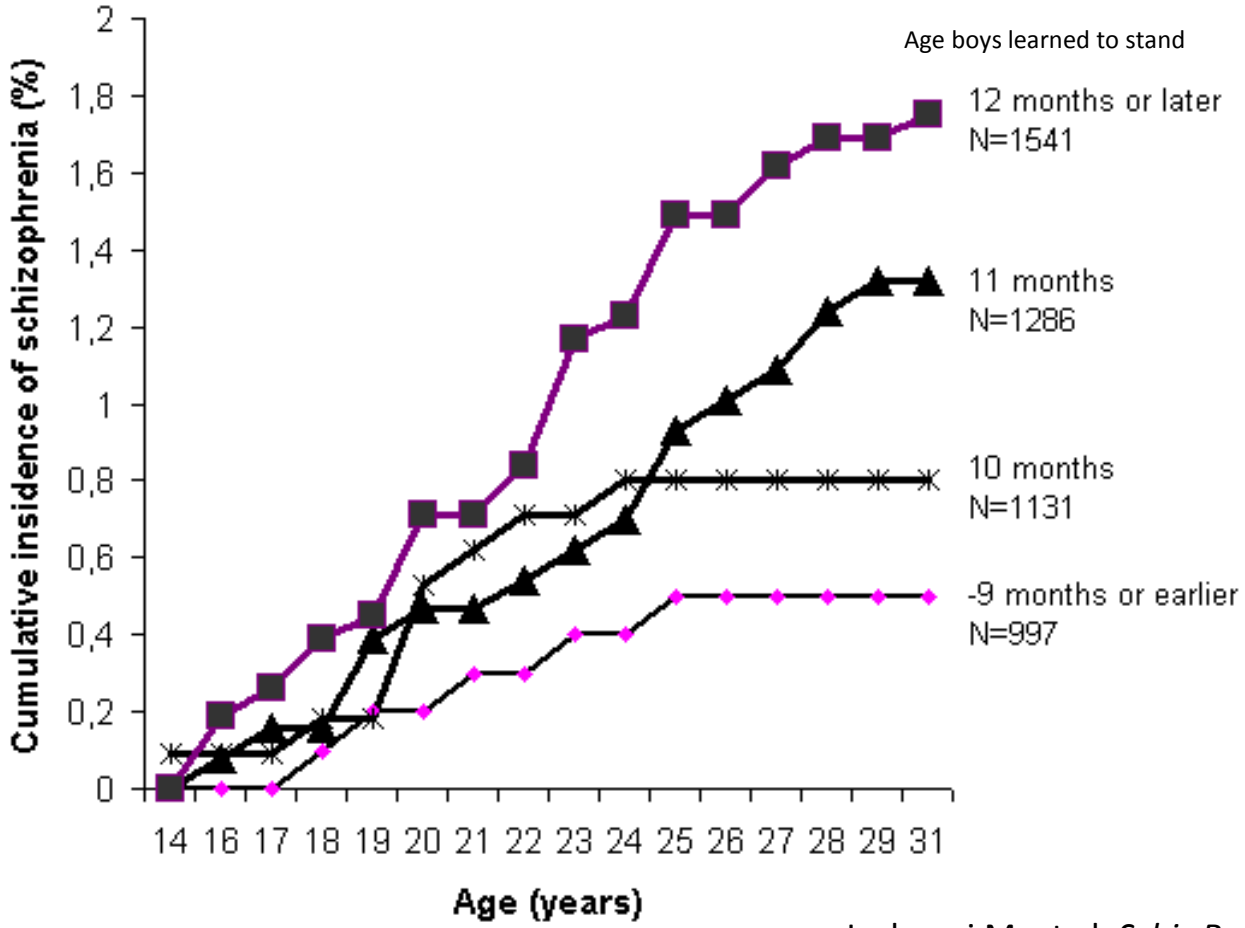
Schizophrenia: The essentials

(ca. end of the 20th century)

- Diagnosis is based on subjective and nonspecific phenomena
- Genes collectively account for most variance in risk
- Environmental adversity in early development accounts for a small increase in risk
- Subtle deviations in childhood development
- Abnormal function of frontal and temporal cortical circuitry
- Subtle nonspecific abnormalities in neuronal architecture
- Antidopaminergic drugs are therapeutic

Developmental antecedents of schizophrenia are well established

The later boys stand during the first year of life, the greater the risk of schizophrenia



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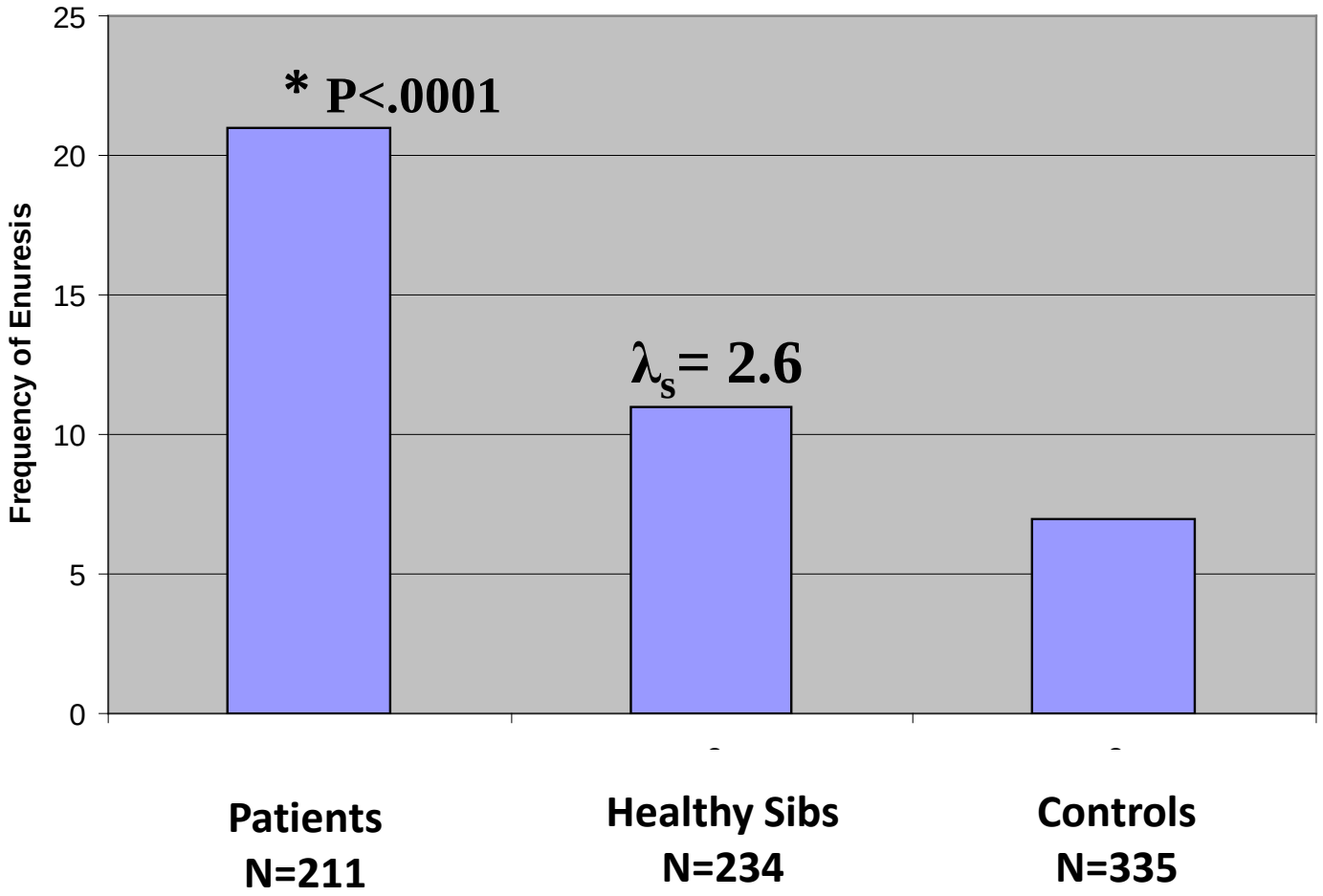
Isohanni M, et al. *Schiz Res*. 2001;52:1-19.

Increased frequency of childhood enuresis in adult patients with schizophrenia



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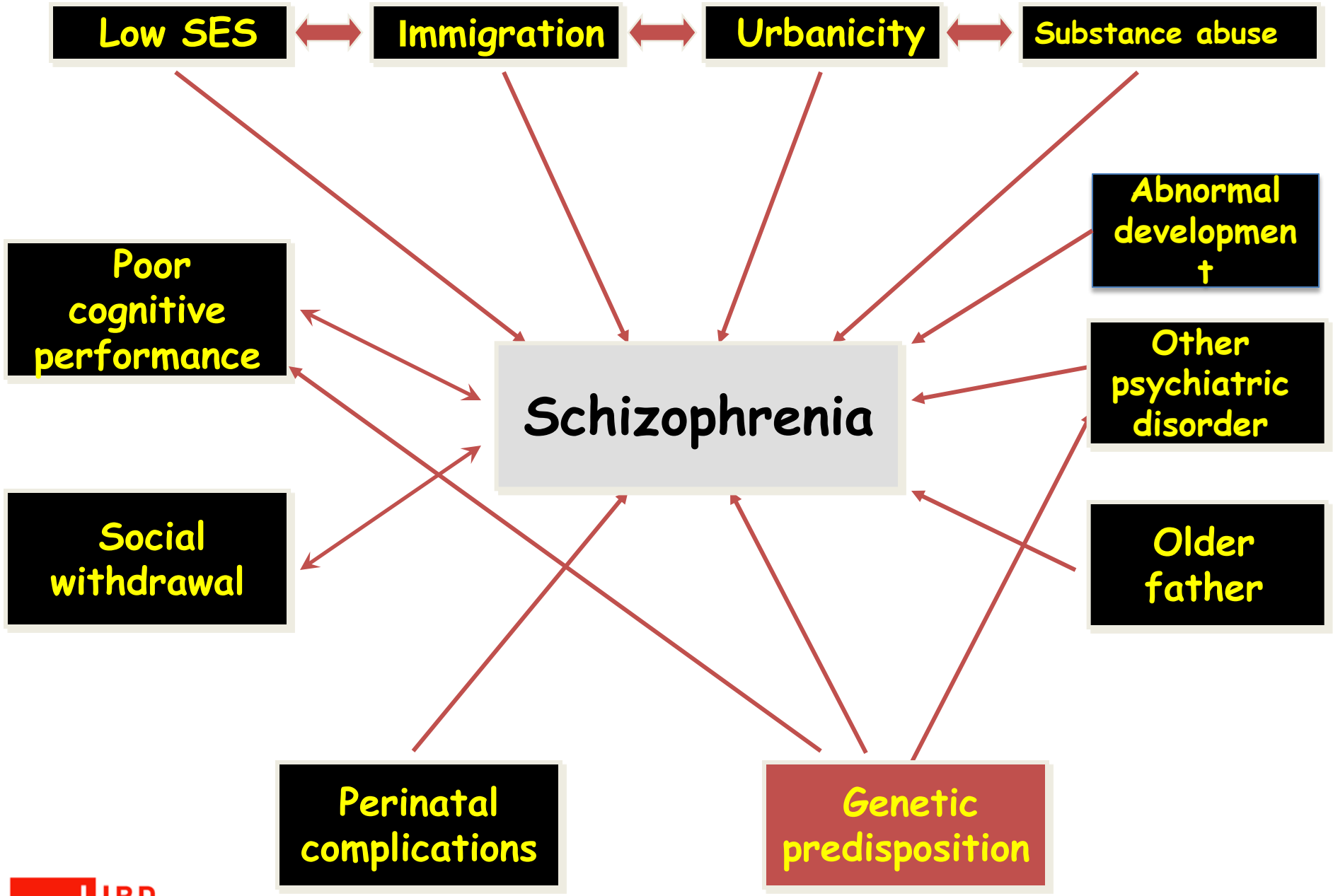
Hyde et al *Brain* 2008



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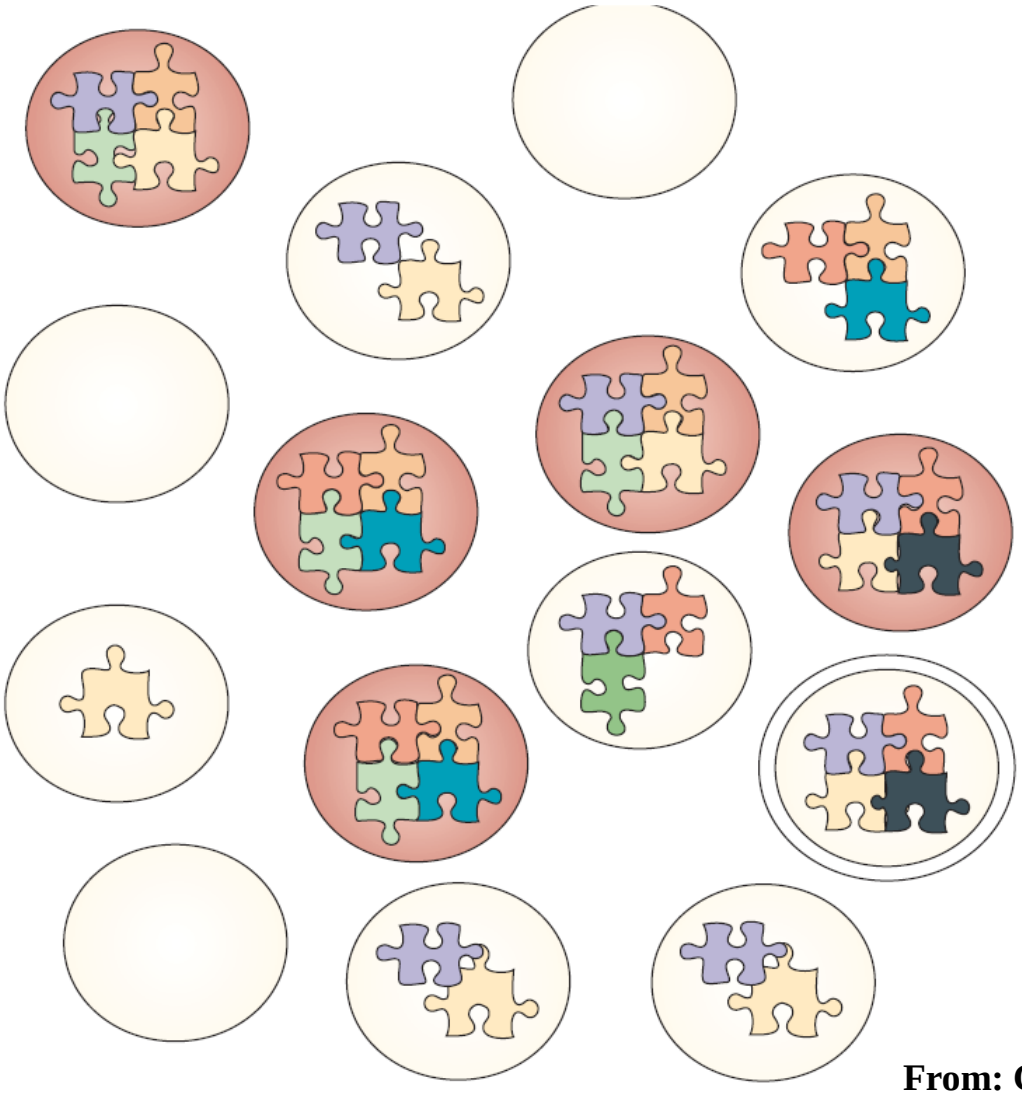
Psychiatric disorders are *polygenic* and genetically *heterogeneous*



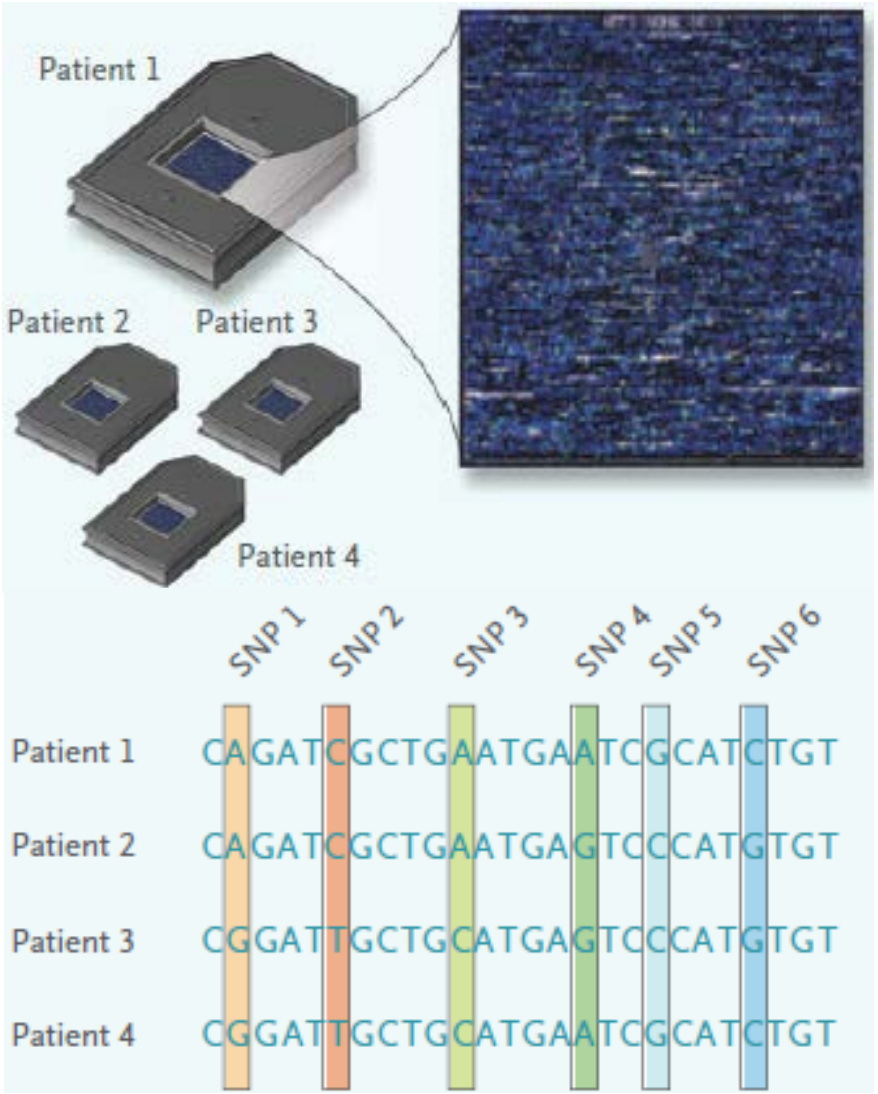
affected person

unaffected

"nonpenetrant"

From: Goldman et al *Nature Rev Genetics* 2005

The genome wide association study (GWAS) of common sequence variants in the genome



PGC1 : can you believe 51,695 subjects?

Ripke et al *Nat Gen* 2011

Table 2 Top genome-wide association results for schizophrenia

SNP	Chr.	Mb	Alleles	Frequency	*P* (GC-adjusted *P*)	OR (95% CI)	Consistency of direction	Gene	Distance (kb)
					5.72×10^{-7} (6.52×10^{-6})	1.14 (1.08–1.19)			
rs1625579	1p21.3[a]	98.3	TG	0.80	**2.65×10^{-6}** (n.a.)	1.11 (1.07–1.16)	+−+++++	*MIR137*	Intragenic
					1.59×10^{-11} (**6.87×10^{-10}**)	1.12 (1.09–1.16)			
					3.09×10^{-6} (2.60×10^{-5})	1.22 (1.13–1.30)			
rs17662626	2q32.3[a]	193.7	AG	0.91	**1.70×10^{-3}** (n.a.)	1.16 (1.06–1.27)	+ −+ +++	*PCGEM1*	343
					4.65×10^{-8} (1.25×10^{-6})	1.20 (1.13–1.26)			
					4.30×10^{-11} (**2.76×10^{-9}**)	1.18 (1.13–1.23)			
rs2021722	6p21.3-p22.1	30.3	CT	0.78	**1.55×10^{-3}** (n.a.)	1.10 (1.03–1.17)	+ ++ −++	*TRIM26*	Intragenic
					2.18×10^{-12} (**2.88×10^{-10}**)	1.15 (1.11–1.19)			
					3.84×10^{-7} (4.71×10^{-6})	1.14 (1.09–1.19)			
rs10503253	8p23.2[a]	4.2	AC	0.19	**7.60×10^{-3}** (n.a.)	1.08 (1.01–1.14)	+ ++ +−+	*CSMD1*	Intragenic
					4.14×10^{-8} (8.98×10^{-7})	1.11 (1.07–1.15)			
					1.45×10^{-8} (3.22×10^{-7})	1.16 (1.11–1.21)			
rs7004633	8q21.3[a]	89.8	GA	0.18	**0.011** (n.a.)	1.05 (1.01–1.10)	++−+++−+	*MMP16*	421
					2.75×10^{-8} (7.03×10^{-7})	1.10 (1.07–1.14)			
					1.58×10^{-7} (2.27×10^{-6})	1.11 (1.07–1.15)			
rs7914558	10q24.32[a]	104.8	GA	0.59	**1.07×10^{-3}** (n.a.)	1.08 (1.03–1.13)	+ ++ +++	*CNNM2*	Intragenic
					1.82×10^{-9} (**3.11×10^{-8}**)	1.10 (1.07–1.13)			
					2.23×10^{-8} (4.58×10^{-7})	1.22 (1.15–1.29)			
rs11191580	10q24.33[a]	104.9	TC	0.91	**5.09×10^{-3}** (n.a.)	1.09 (1.02–1.16)	++++++++	*NT5C2*	Intragenic
					1.11×10^{-8} (3.72×10^{-7})	1.15 (1.10–1.20)			
					2.91×10^{-8} (5.69×10^{-7})	1.20 (1.13–1.26)			
rs548181	11q24.2	125.0	GA	0.88	0.068 (n.a.)	1.04 (0.98–1.11)	+++++−+	*STT3A*	1
					8.87×10^{-7} (1.74×10^{-5})	1.11 (1.07–1.16)			
					1.00×10^{-6} (1.03×10^{-5})	1.10 (1.06–1.14)			
rs12966547	18q21.2	50.9	GA	0.58	**2.29×10^{-5}** (n.a.)	1.08 (1.04–1.12)	+−+++++	*CCDC68*	126
					2.60×10^{-10} (**5.99×10^{-9}**)	1.09 (1.06–1.12)			
					2.35×10^{-8} (4.78×10^{-7})	1.40 (1.28–1.52)			
rs17512836	18q21.2	51.3	CT	0.02	0.085 (n.a.)	1.08 (0.96–1.20)	−++++++	*TCF4*	Intragenic
					1.05×10^{-6} (2.86×10^{-5})	1.23 (1.14–1.31)			

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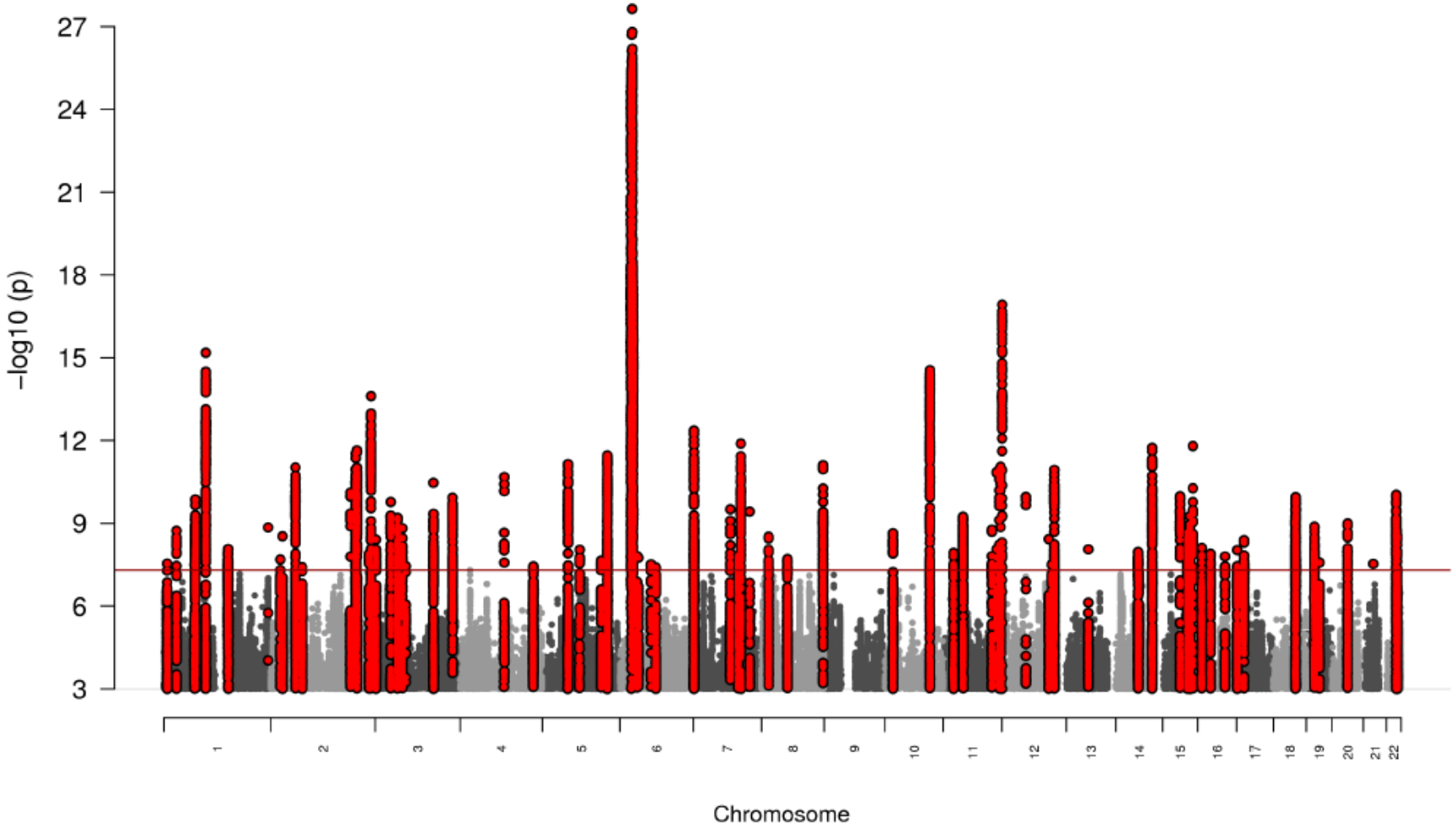
PGC 3 – let's try *70,000* subjects!
Now over 70 loci are GWAS "significant"



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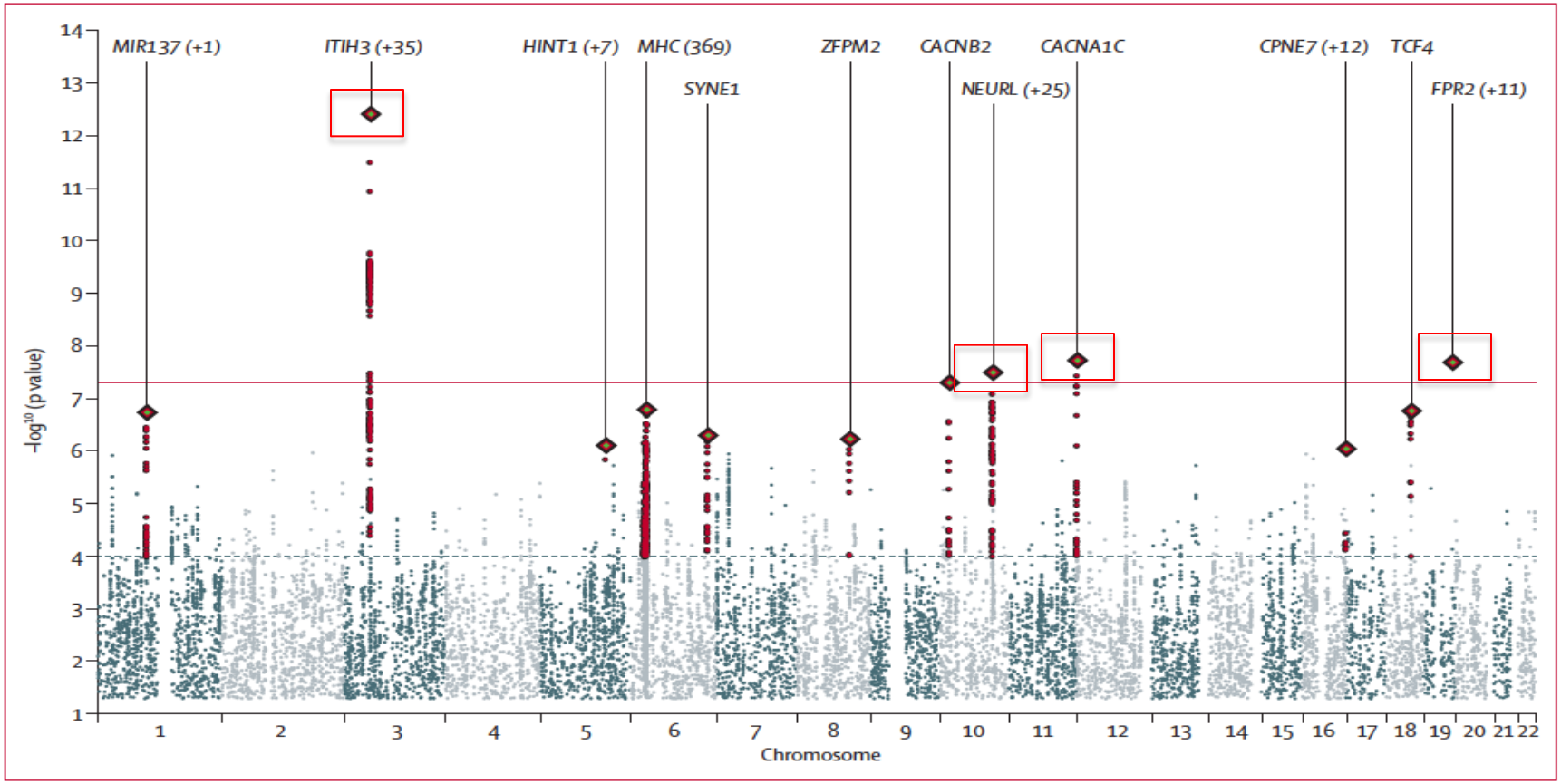
Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis

*Cross-Disorder Group of the Psychiatric Genomics Consortium**



Four "loci" identified in 61,220 subjects

Lancet 2013

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

*Cross-Disorder Group of the Psychiatric Genomics Consortium**

N= 61,220 subjects (33,332 cases)

	Chromosome	Base-pair position*	Nearest gene	Alleles	Frequency†	Imputation quality score (INFO)	p value	OR (95% CI)‡
rs2535629	3	52808259	*ITIH3* (+ many)	G/A	0·651	0·942	$2{\cdot}54\times10^{-12}$	1·10 (1·07–1·12)
rs11191454	10	104649994	*AS3MT* (+ many)	A/G	0·910	1·01	$1{\cdot}39\times10^{-8}$	1·13 (1·08 –1·18)
rs1024582	12	2272507	*CACNA1C*	A/G	0·337	0·98	$1{\cdot}87\times10^{-8}$	1·07 (1·05-1·10)
rs2799573	10	18641934	*CACNB2*	T/C	0·715	0·825	$4{\cdot}29\times10^{-8}$	1·08 (1·05-1·12)

***Lancet* 2013**

Compare with: Sklar et al *Nature Genetics* 2011, N=11,974 cases

Table 3 Association results for the primary GWAS, replication and combined samples

					Primary GWAS		Replication[a]		Combined GWAS and replication		
SNP	Chr.[b]	Position[c]	A1	A2	P_{GC}	OR[d]	$P_{1\text{-sided}}$	OR	P_{GC}	OR	Genes in the LD region
rs4765913	12	2,290,157	A	T	6.50×10^{-6}	1.15	1.60×10^{-4}	1.13	**1.52×10^{-8}**	**1.14**	*CACNA1C*

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An Inconvenient Question:

Why are the clinical associations so weak?

Some answers:

Heterogeneity

Environmental modification

rare variants

epigenetics

Epistasis

GENES DO NOT ENCODE FOR PSYCHIATRIC SYNDROMES

A clinician's perspective:

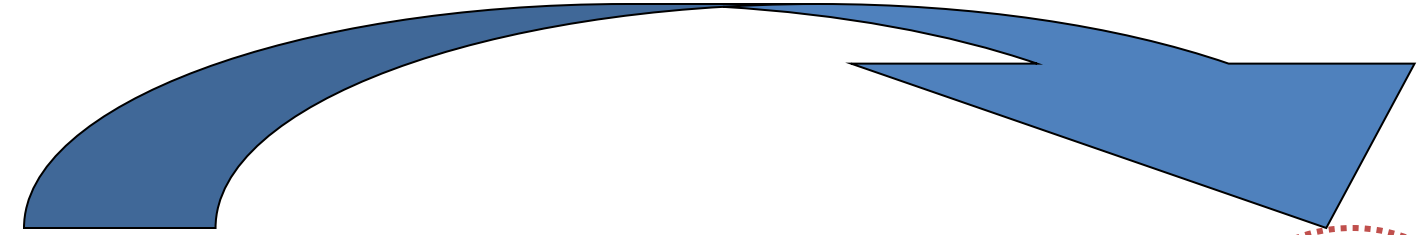
Three key points in this talk

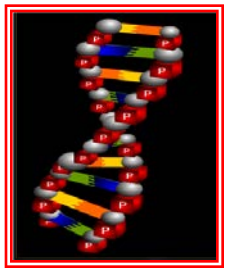
1. **The genes for psychiatric disorders are not for psychiatric disorders.**

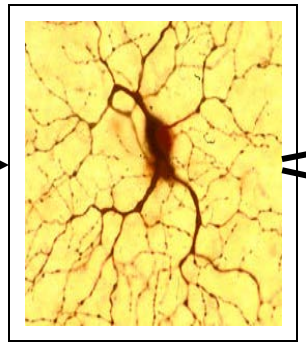
2. **Genetic risk is critically dependent on context (both genetic and environmental).**

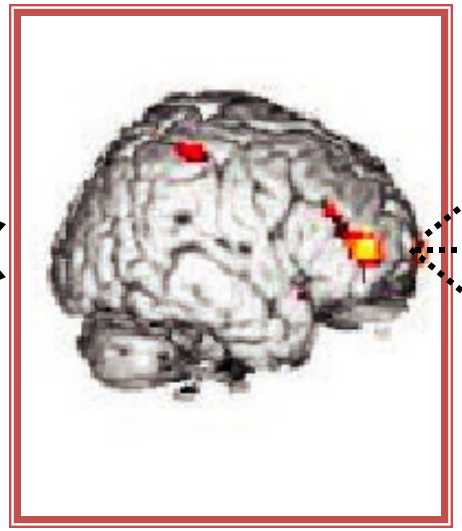
2. **Genes impact on outcome and treatment response and will lead to new therapies.**

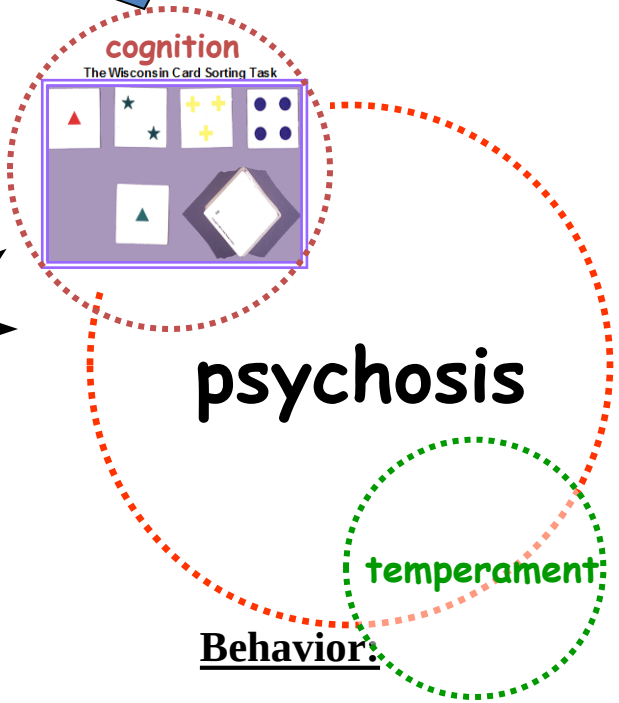
Schizophrenia: genes and associated neurobiology











Genes:

multiple susceptibility alleles each of small effect

Cells:

subtle molecular abnormalities

Systems:

abnormal information processing

Behavior:

complex functional interactions and emergent phenomena

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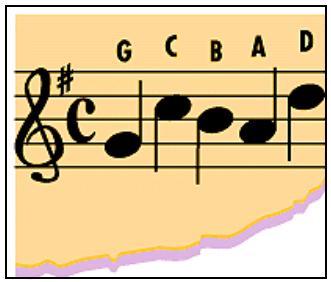
"The path from changes in the score (DNA code) to changes in the music (behavior)"



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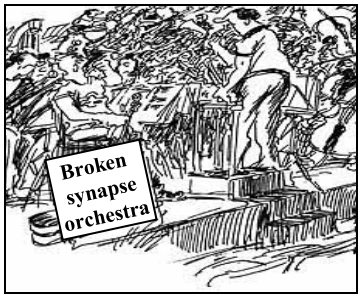

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Genes:

multiple susceptibility alleles each of small effect

Cells:

subtle synaptic molecular abnormalities

Distributed Neural Systems:

abnormal information processing

Perturbed Cognition:

as an emergent phenomena

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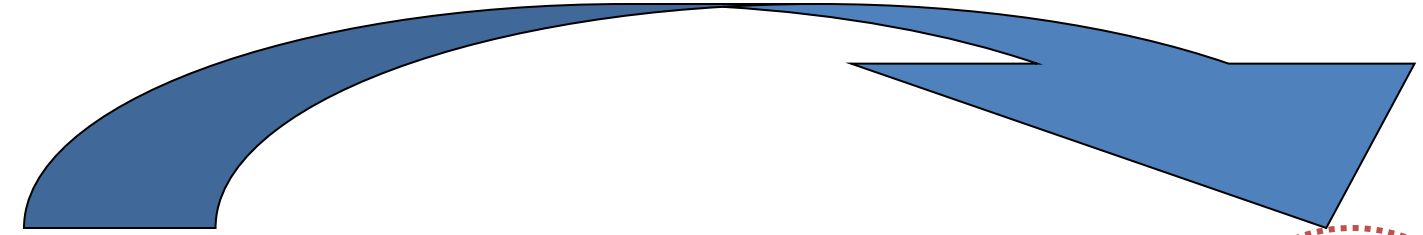
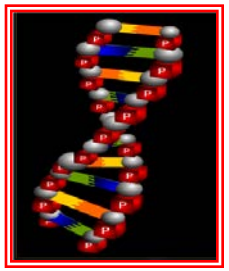
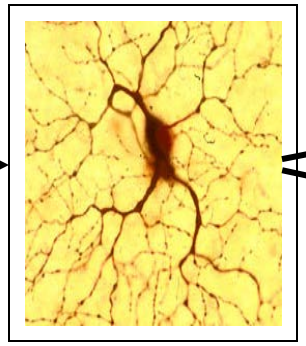
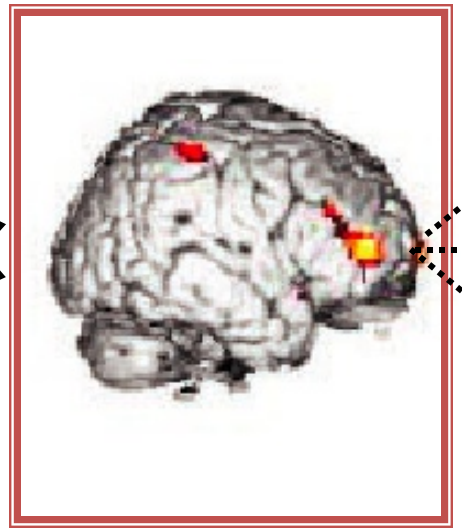
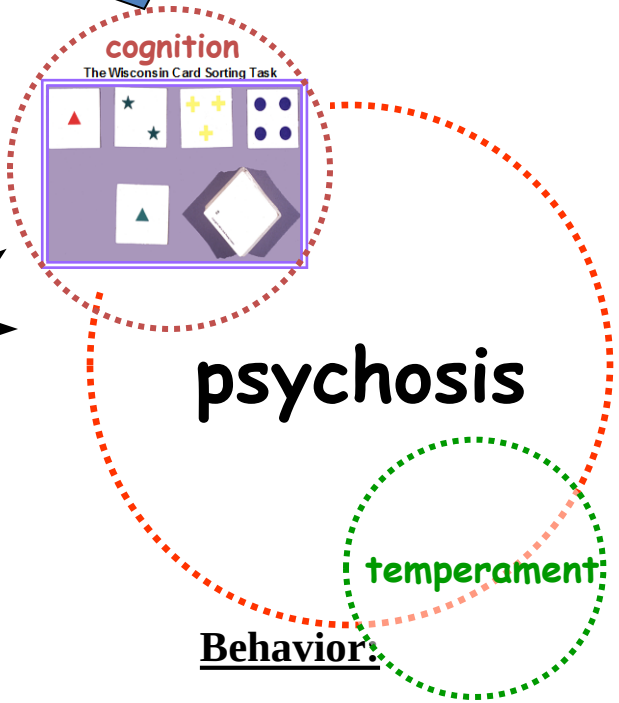
Schizophrenia: genes and associated neurobiology











Genes:

multiple susceptibility alleles each of small effect

Cells:

subtle molecular abnormalities

Systems:

abnormal information processing

Behavior:

complex functional interactions and emergent phenomena

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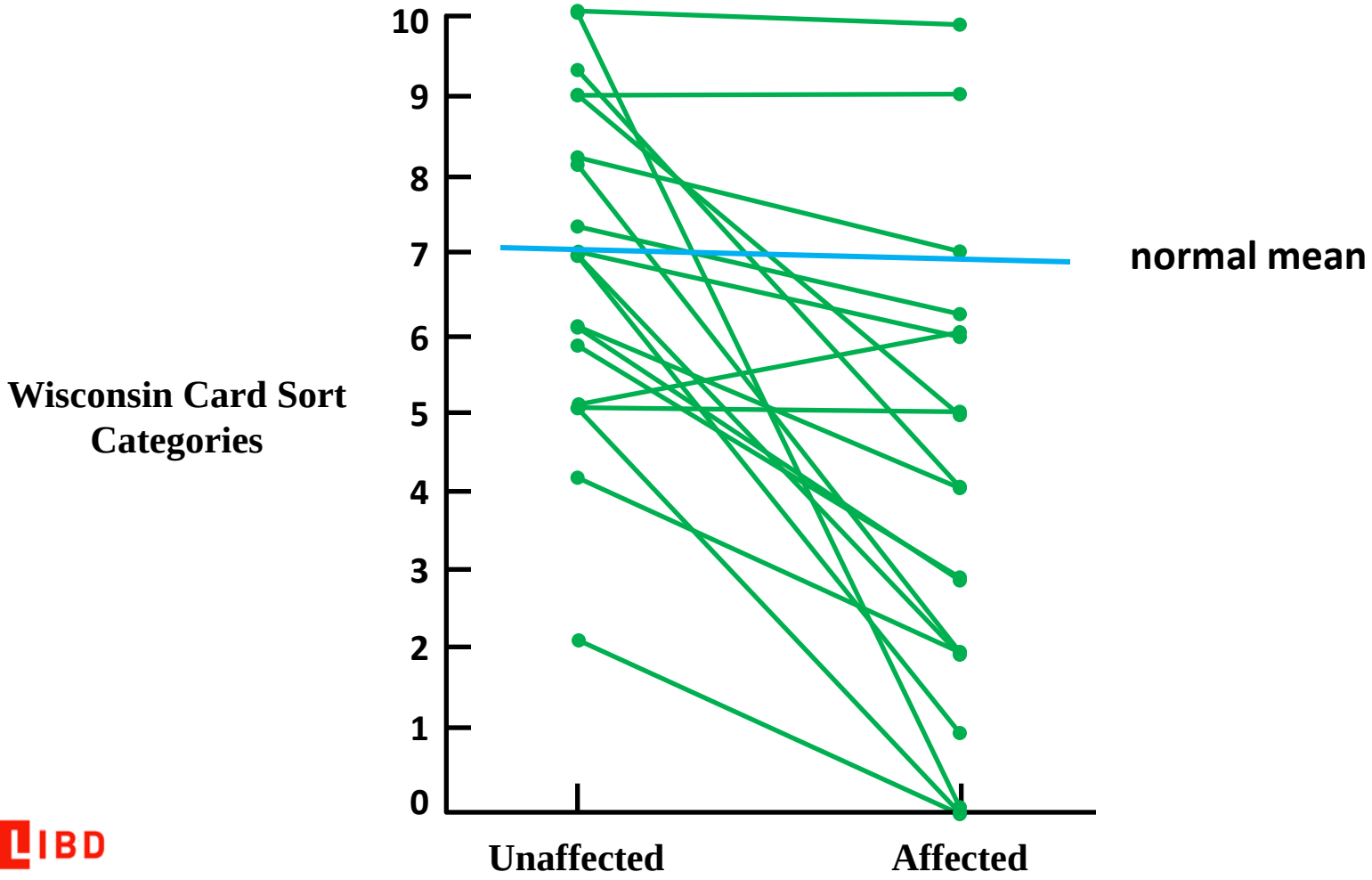
Executive cognition in MZ twins *discordant* for schizophrenia



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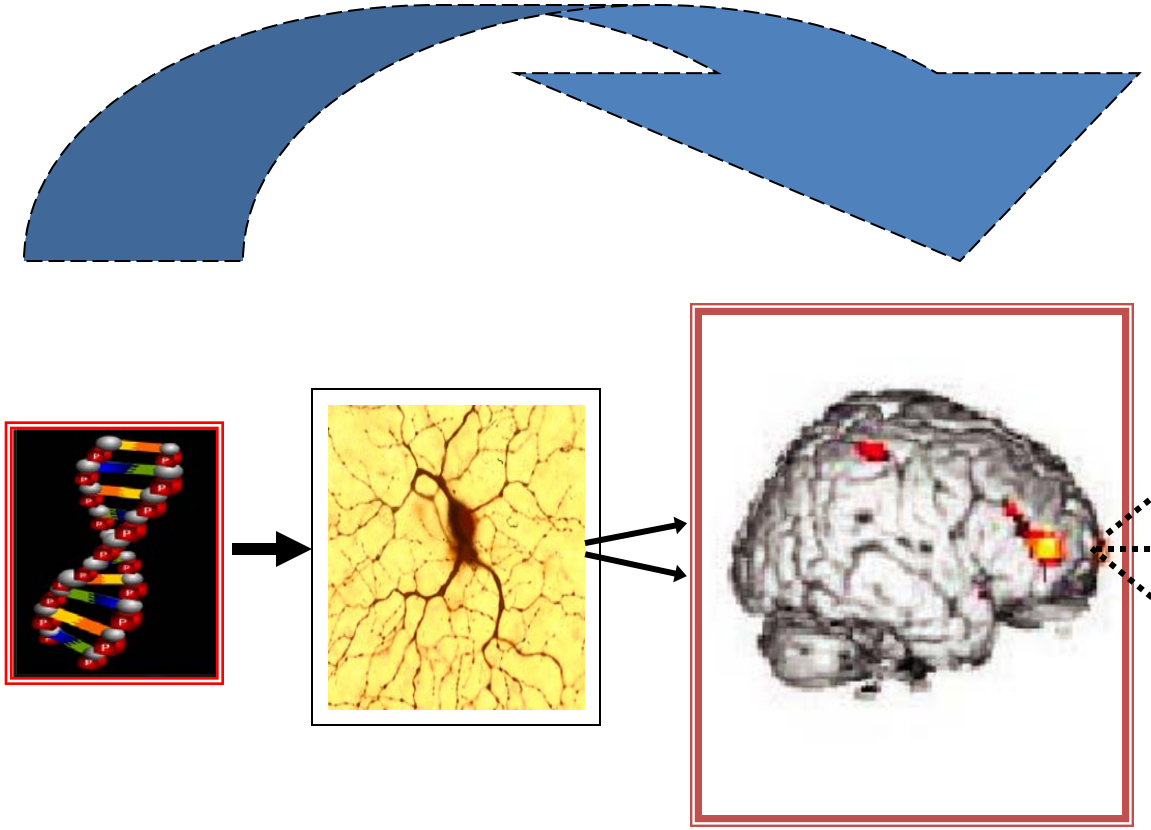
Goldberg et al *Arch Gen Psych* 1990

Abnormal behavior reflects abnormal brain function



Genes:

risk associated genotypes

Cells:

molecular biology

Systems:

abnormal information processing

Behavior:

complex functional interactions and emergent phenomena

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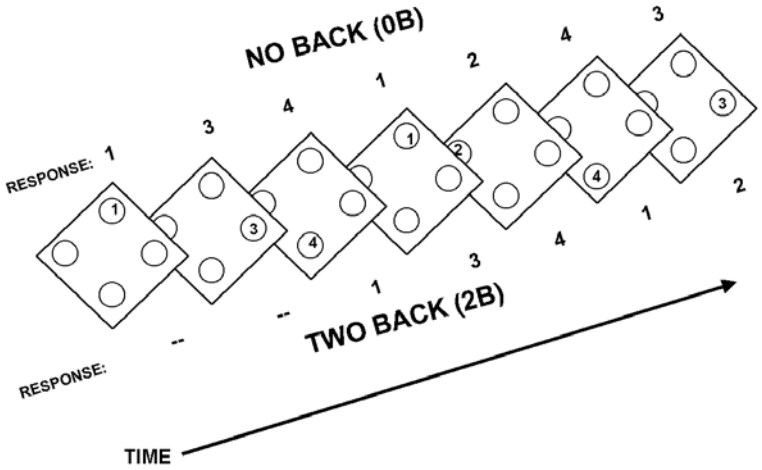
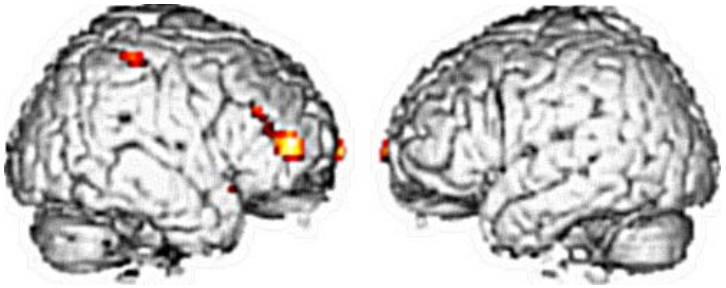
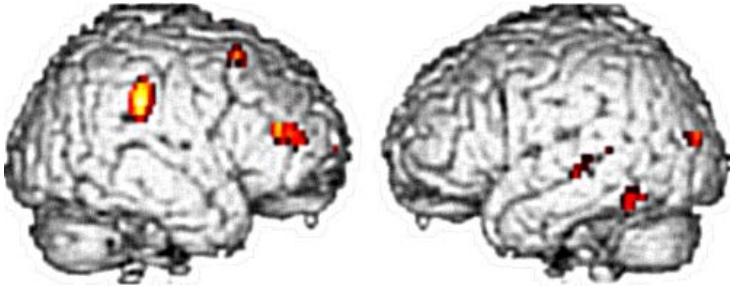
Abnormal prefrontal “efficiency“ : A schizophrenia intermediate phenotype



The “N Back” working memory task



fMRI



Patients > Controls
(N=13) (N=18)

Healthy Siblings > Controls
(N=48) (N=33)

Callicott *et al. Cereb Cortex* 2000

Callicott *et al. Am J Psychiatry* 2003

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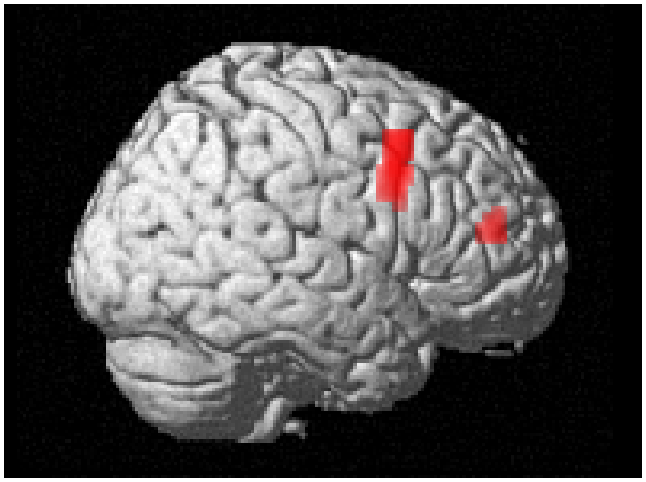
Bipolar/schizophrenia risk associated gene *CACNA1C* modulates cortical efficiency during working memory in normal subjects

rs1006737: AA >GG+GA



N=316, p=.01 FDR corrected

Extrapolated to N=10,000, p< 4.87e-^{109}

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Bigos et al *Arch Gen Psychiatry* 2010

A clinician's perspective:

Three key points in this talk

1. The genes for psychiatric disorders are not for psychiatric disorders.

2. **Genetic risk is critically dependent on context (both genetic and environmental).**

2. Genes will impact on outcome and treatment response and lead to new therapies.

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Genes also interact with the environment to modify the expression of their individual effects. This can lead to exaggerated, compensated, or novel effects.

AJP in Advance. Published September 2, 2011 (doi: 10.1176/appi.ajp.2011.11010011)

Article

Increased Risk of Schizophrenia From Additive Interaction Between Infant Motor Developmental Delay and Obstetric Complications: Evidence From a Population-Based Longitudinal Study

Mary C. Clarke, Ph.D.

Antti Tanskanen, Ph.Lic.

Matti Huttunen, M.D., Ph.D.

David A. Leon, Ph.D.

Robin M. Murray, M.D., D.Sc.

Peter B. Jones, M.D., Ph.D.

Mary Cannon, M.D., Ph.D.

Objective: Obstetric complications and developmental delay are well-established risk factors for schizophrenia. The authors investigated whether these risk factors interact in an additive manner to further increase risk for schizophrenia.

Method: The study population encompassed all individuals born in Helsinki between 1962 and 1969 who had developmental records archived in the Helsinki City Archives. Through linkage between the Finnish Population Register, the Finnish Hospital Discharge Register, and the Child Health Archives, child health cards were traced for 189 individuals who had received a diagnosis of schizophrenia and 189 healthy comparison subjects, indi-

Detailed developmental data from the first year of life were extracted.

Results: Delayed attainment of milestones in infancy significantly increased the risk of later development of schizophrenia in a dose-response manner. There was no significant main effect of obstetric complications on risk for schizophrenia and no significant association between obstetric complications and subsequent developmental delay. However, the additive effect of obstetric complications and delayed attainment of developmental milestones significantly increased the risk of schizophrenia beyond that associated with each factor independently (odds ratio=4.6, 95% confidence interval=1.3–17.2).

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Interaction of serious OC's with SNPs in genes associated with anoxia-ischemia

Table 1 Odds ratios (95% confidence interval) for serious obstetric complications (OCs) and minor allele carrier status

SNP	*Gene*	*OC status*	*OR*	*95% CI*	*OR* P-*value*	N *families*[a]	N *minor allele transmissions (%)*	*LRT* P-*value*
rs2494735	AKT1	Absent	1.0	—	—	59	36 (61.0)	—
		Present	7.18	(0.91, 56.75)	0.062	17	15 (88.2)	0.037
rs3803300	AKT1	Absent	1.0	—	—	78	11 (14.1)	—
		Present	3.89	(0.83, 18.20)	0.085	24	14 (58.3)	0.012
rs1130233	AKT1	Absent	1.0	—	—	71	31 (43.7)	—
		Present	3.97	(1.13, 13.92)	0.031	24	16 (66.7)	0.02
rs2049046	BDNF	Absent	1.0	—	—	73	23 (31.5)	—
		Present	0.15	(0.032, 0.73)	0.019	21	3 (14.3)	0.011
ss76882600	BDNF	Absent	1.0	—	—	74	39 (52.7)	—
		Present	12.45	(1.63, 94.60)	0.015	23	17 (73.9)	0.028
rs875462	DTNBP1	Absent	1.0	—	—	61	39 (63.9)	—
		Present	9.49	(1.23, 73.30)	0.031	18	14 (77.8)	0.025
rs7808623	GRM3	Absent	1.0	—	—	72	22 (30.6)	—
		Present	3.39	(0.95, 12.17)	0.061	23	12 (52.2)	0.035

[a]Number of families differs for each SNP because only fully genotyped families were used in analysis.

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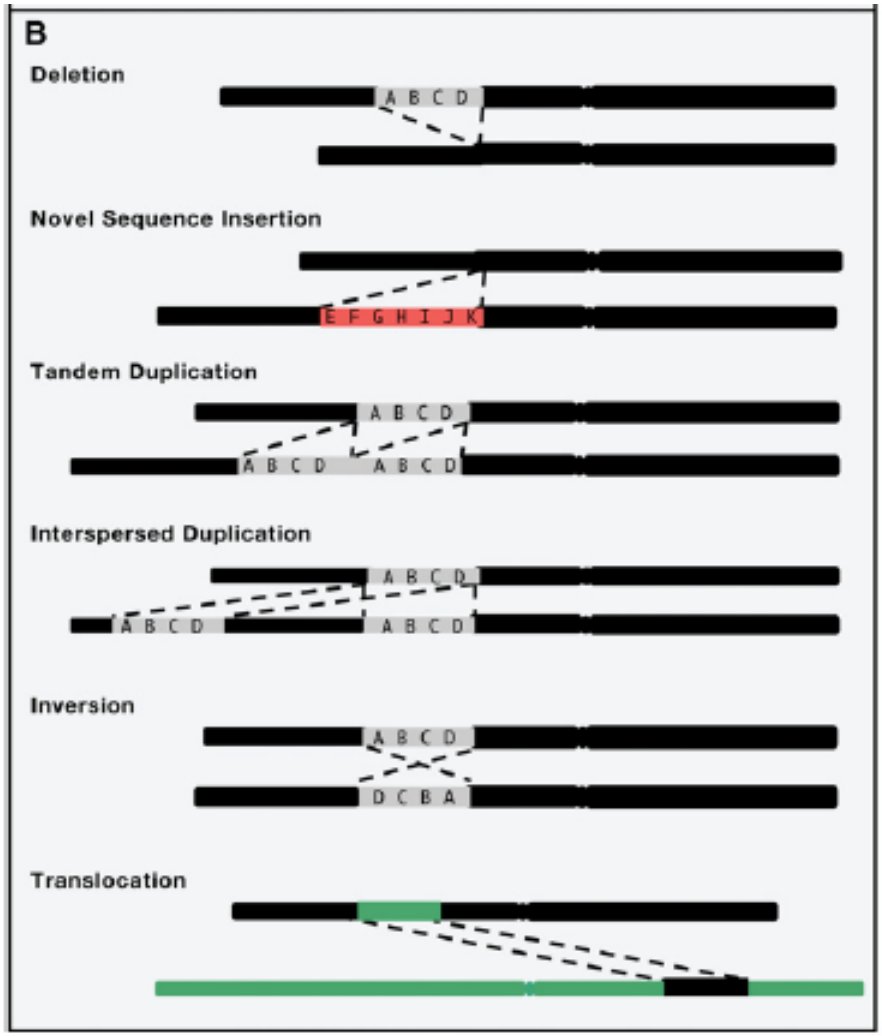
Nicodemus et al. *Mol Psychiatry* 2008.

Large structural variations in the DNA molecule ("CNVs") occur during DNA replication



Malhotra and Sebat *Cell* 2012

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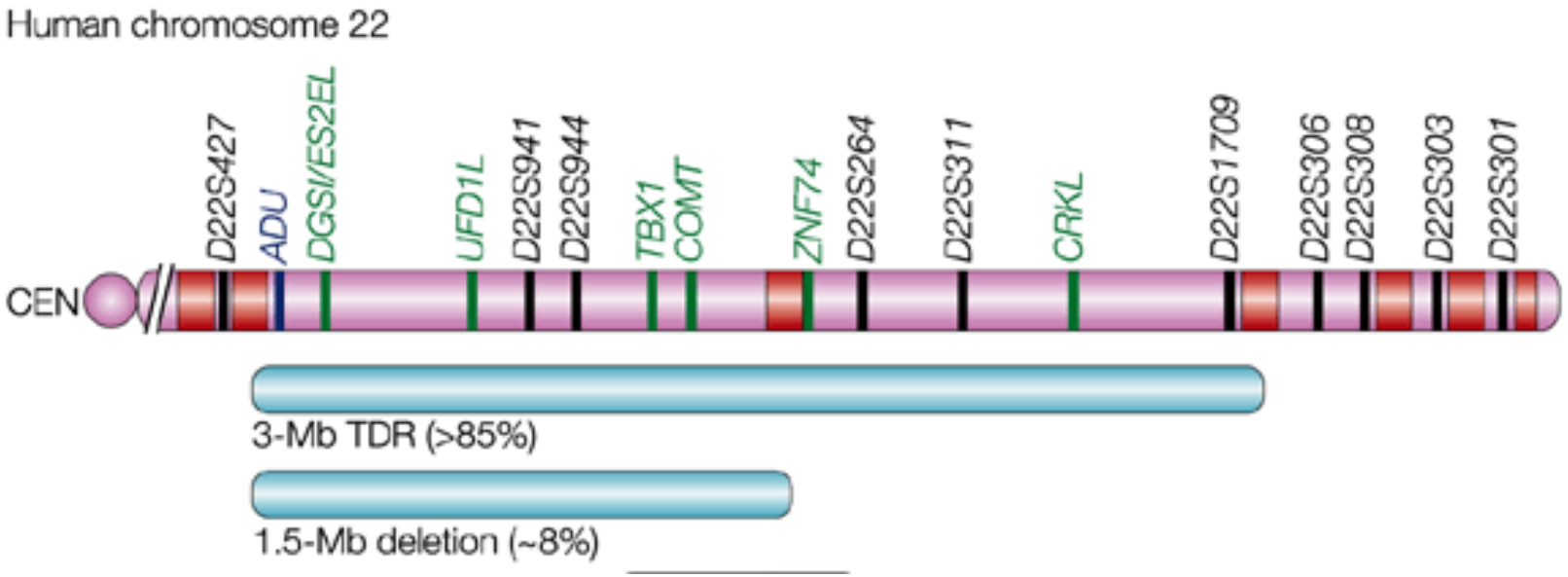
22q11 Hemideletion Syndrome: Velo-Cardio-Facial Syndrome (VCFS)



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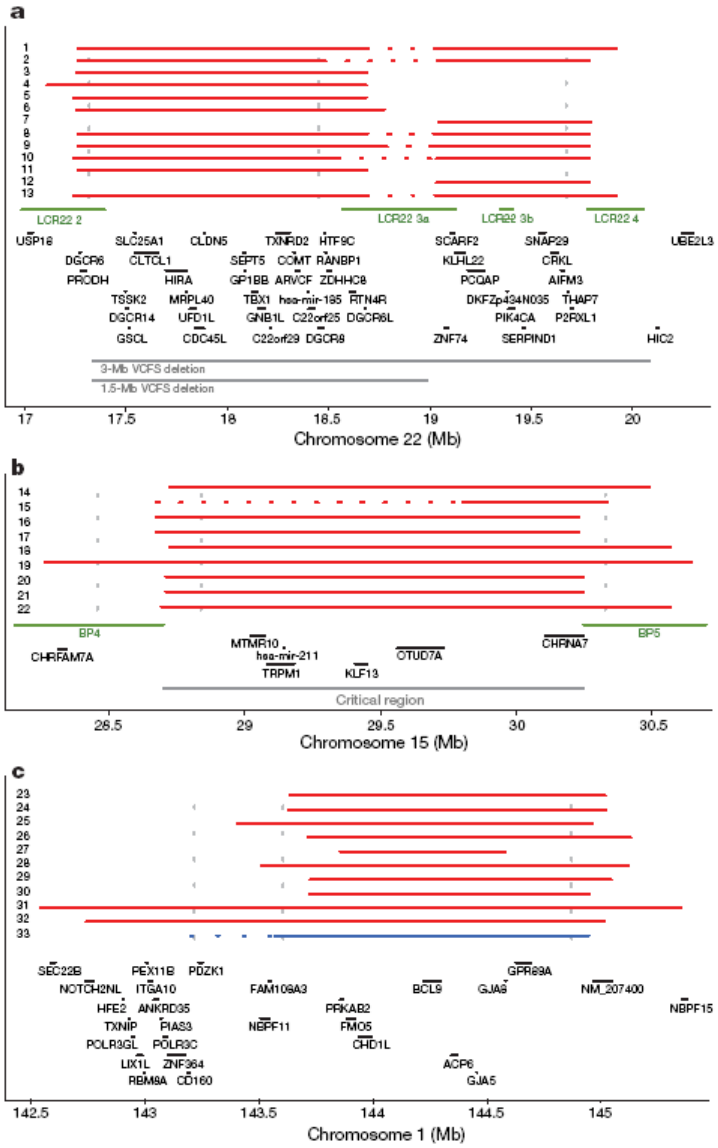
Specific recurrent CNVs are found in 2-5% of patients with the diagnosis of schizophrenia



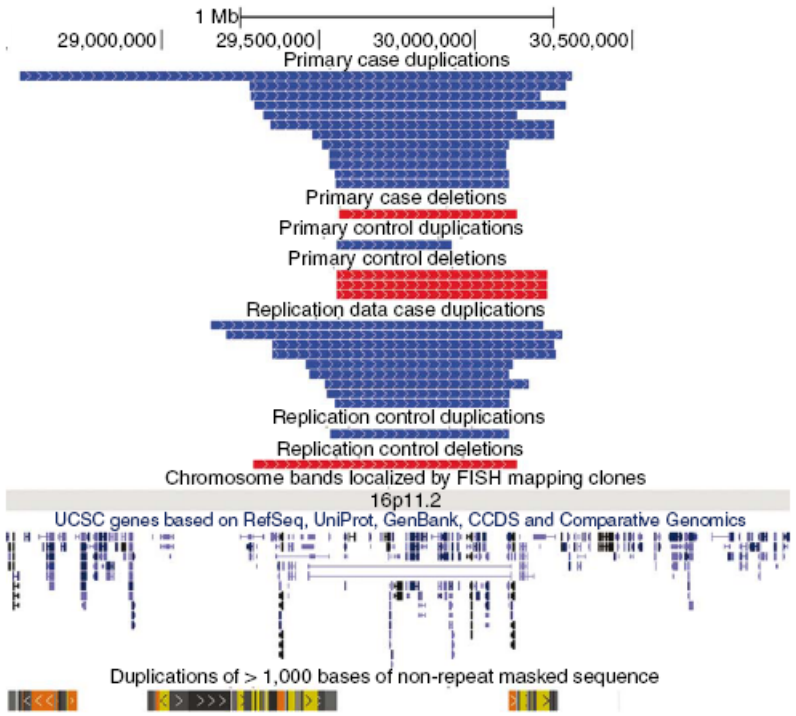


Figure 1 Microduplications and microdeletions at 16p11.2

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ISC *Nat Genetics* 2008

McCarthy et al *Nat Genetics* 2009

A clinician's perspective:

Three key points in this talk

1. The genes for psychiatric disorders are not for psychiatric disorders.

2. Genetic risk is critically dependent on context (both genetic and environmental).

2. **Genes impact on outcome and treatment response and will lead to new therapies.**

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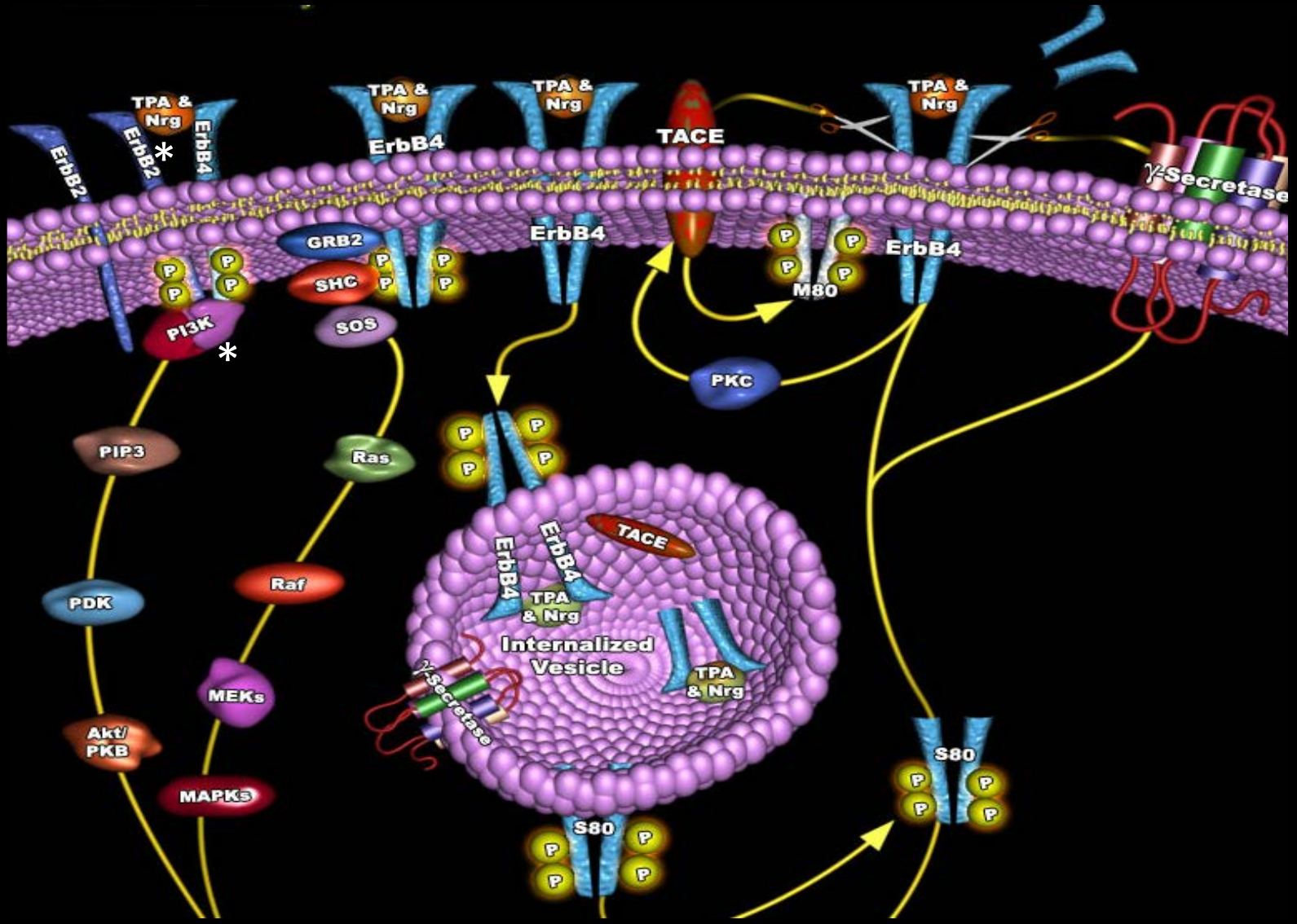
Genes are keys to the biology of cells



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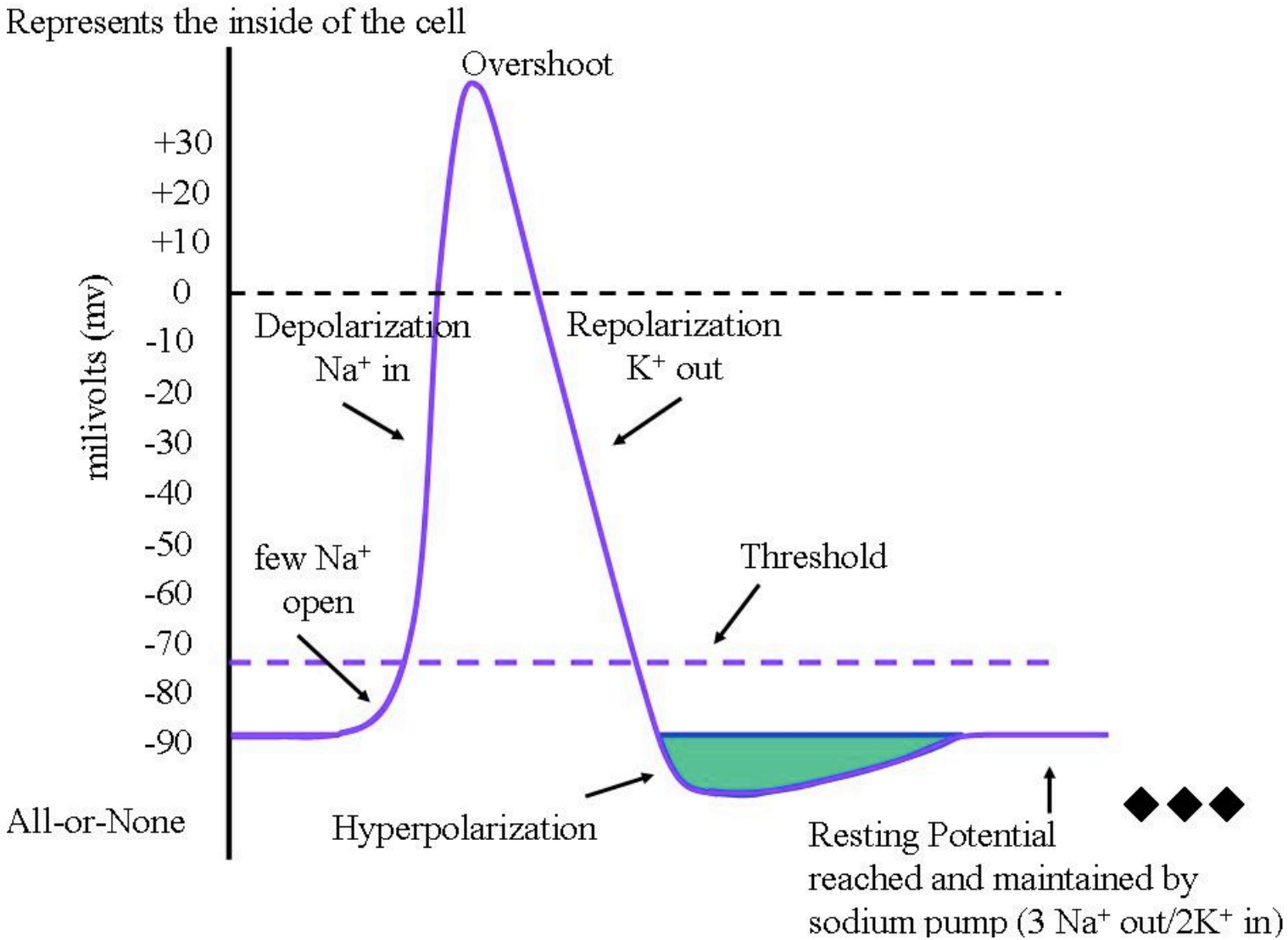
Na^+-K^+ currents and the action potential



Article

Genetic Variation in *KCNH2* Associated With Expression in the Brain of a Unique hERG Isoform Modulates Treatment Response in Patients With Schizophrenia

José A. Apud, M.D., Ph.D.

Fengyu Zhang, Ph.D.

Heather Decot, B.S.

Kristin L. Bigos, Ph.D.

Daniel R. Weinberger, M.D.

Objective: Antidopaminergic drugs bind to hERG1 potassium channels encoded by the gene *KCNH2*, which accounts for the side effect of QT interval prolongation. *KCNH2* has also been associated with schizophrenia risk, and risk alleles predict increased expression of a brain-selective isoform, *KCNH2* 3.1, that has unique physiological properties. The authors assessed whether genetic variation associated with *KCNH2* 3.1 expression influences the therapeutic effects of antipsychotic drugs.

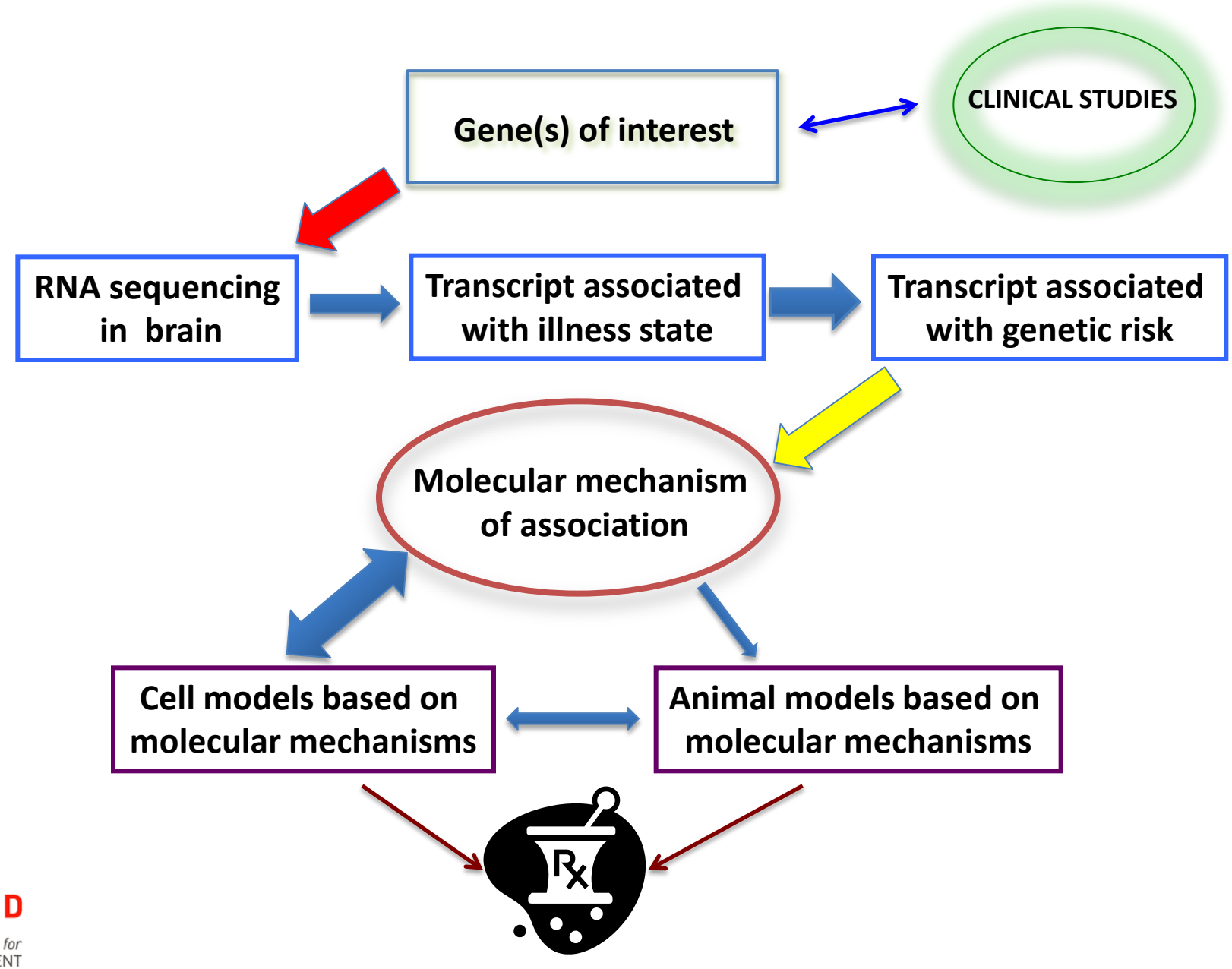
Method: The authors performed a pharmacogenetic analysis of antipsychotic treatment response in patients with schizophrenia using data from two independent studies: a National Institute of Mental Health (NIMH) double-blind, placebo-controlled inpatient crossover trial (N=54) and the multicenter outpatient Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) study (N=364). The *KCNH2* genotype that was previously associated with increased expression of KCNH2 3.1 in the brain was treated as a predictor variable. Treatment-associated changes in symptoms were evaluated in both groups with the Positive and Negative Syndrome Scale. The authors also analyzed time to discontinuation in the olanzapine arm of the CATIE study.

Results: In the NIMH study, individuals who were homozygous for the *KCNH2* 3.1 increased expression-associated T allele of rs1036145 showed significant improvement in positive symptoms, general psychopathology, and thought disturbance, while patients with other genotypes showed little change. In the CATIE study, analogous significant genotypic effects were observed. Moreover, individuals who were homozygous for the T allele at rs1036145 were one-fifth as likely to discontinue olanzapine.

Conclusions: These consistent findings in two markedly different treatment studies support the hypothesis that hERG1-mediated effects of antipsychotics may not be limited to their potential cardiovascular side effects but may also involve therapeutic actions related to the brain-specific 3.1 isoform of *KCNH2*.

(Am J Psychiatry 2012; 169:725–734)

A Roadmap for Genes to Drugs



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Genes, brain and drugs: Conclusions...

- **Most complex behaviors are the result of multiple factors that interact biologically.**
- **Genes are the first objective clues to the causative mechanisms of psychiatric disorders.**
- **There are many developmental pathways to what we call schizophrenia.**
- **Genes for schizophrenia likely have their effects on risk by influencing brain development.**
- **The genetics of psychiatric illness is *the* game changer both in understanding mechanisms and in finding therapeutic targets based on causation, not phenomenology.**

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