Personalized Medicine: Implications and Future

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Disclosure Information

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- Novartis
- Organon
- Otsuka
- Pfizer
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- SchéringPlough
- Roche
- Wyeth

Consultancy/Advisory Board/Honoraria

- Arena Pharmaceuticals
- AstraZeneca
- Bristol-Myers Squibb
- Janssen Pharmaceutica
- Novartis
- Organon
- Otsuka
- Pfizer
- Praecis
- Roche
- Vanda

Speakers Bureau

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- Novartis
- Pfizer
- Otsuka

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Outline

Personalized medicine - What is it? A personal view.

Candidate genes to predict efficacy and side-effects

GWAS approaches to predict efficacy and side-effects

Statistical issues

Implications for drug development

Conclusions and Questions

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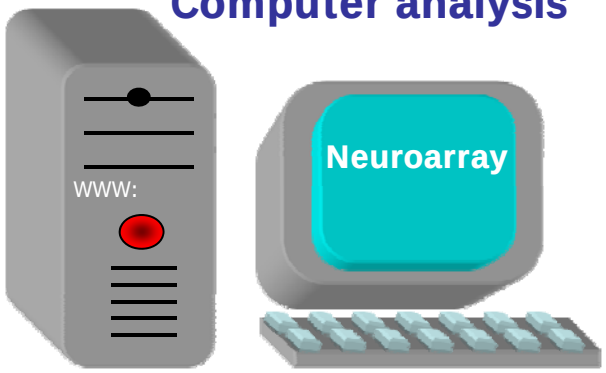
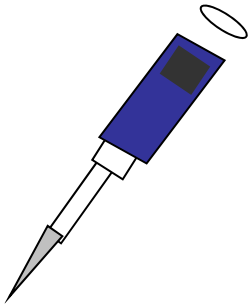
Personalized medicine in the near future

Probabilities of medication response and development of side-effects

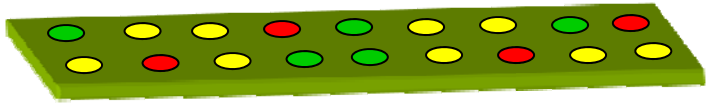
	Efficacy	Negative	Cognitive	DM	Weight	Suicide
Clozapine	90	80	25	50	85	2
Olanzapine	80	70	20	70	90	4
Iloperidone	95	75	30	20	10	?



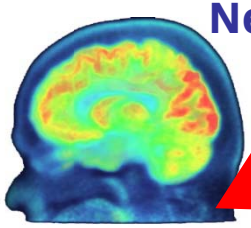
Computer analysis



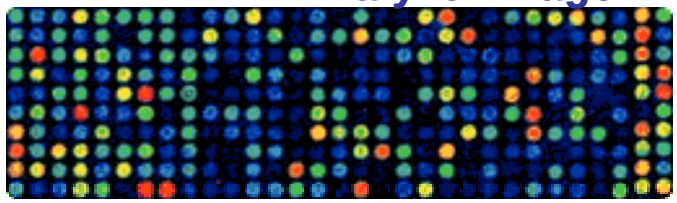
Blood sample in physician's office



Gene Chip



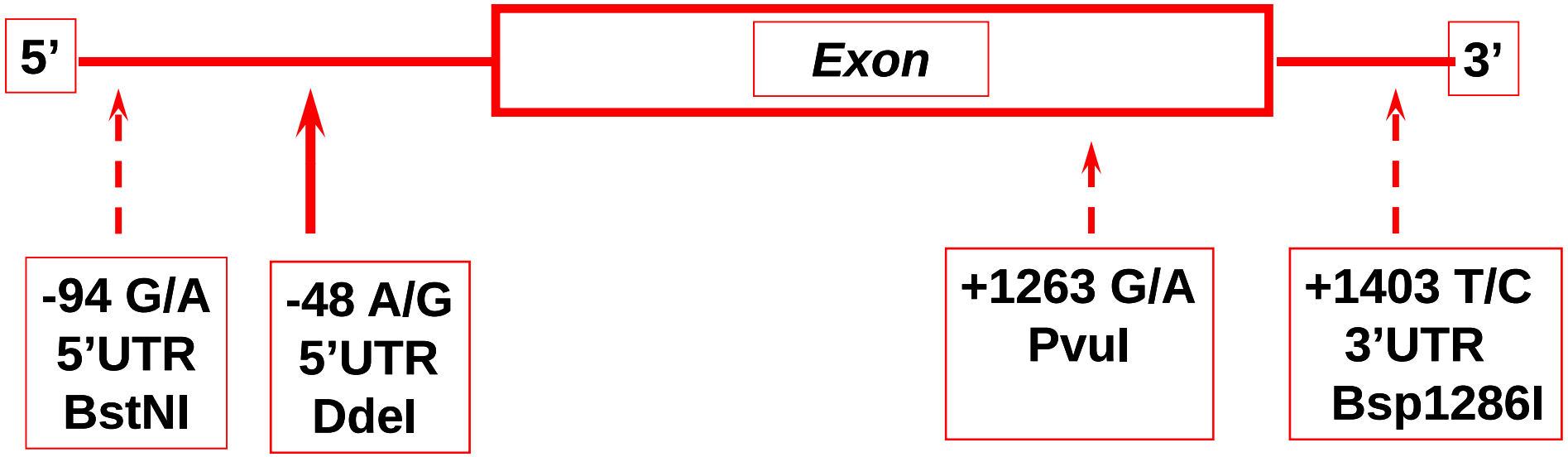
Neuroimaging



Analyze Image

after Potkin et al 2002

DRD1 Polymorphisms



D1 receptor most prevalent dopamine receptors in human cortex

Putative regulatory region of DRD1

Allele 1 (A) is more common (~65% in our Caucasian sample & ~90% in our African American sample) than allele 2 (G)

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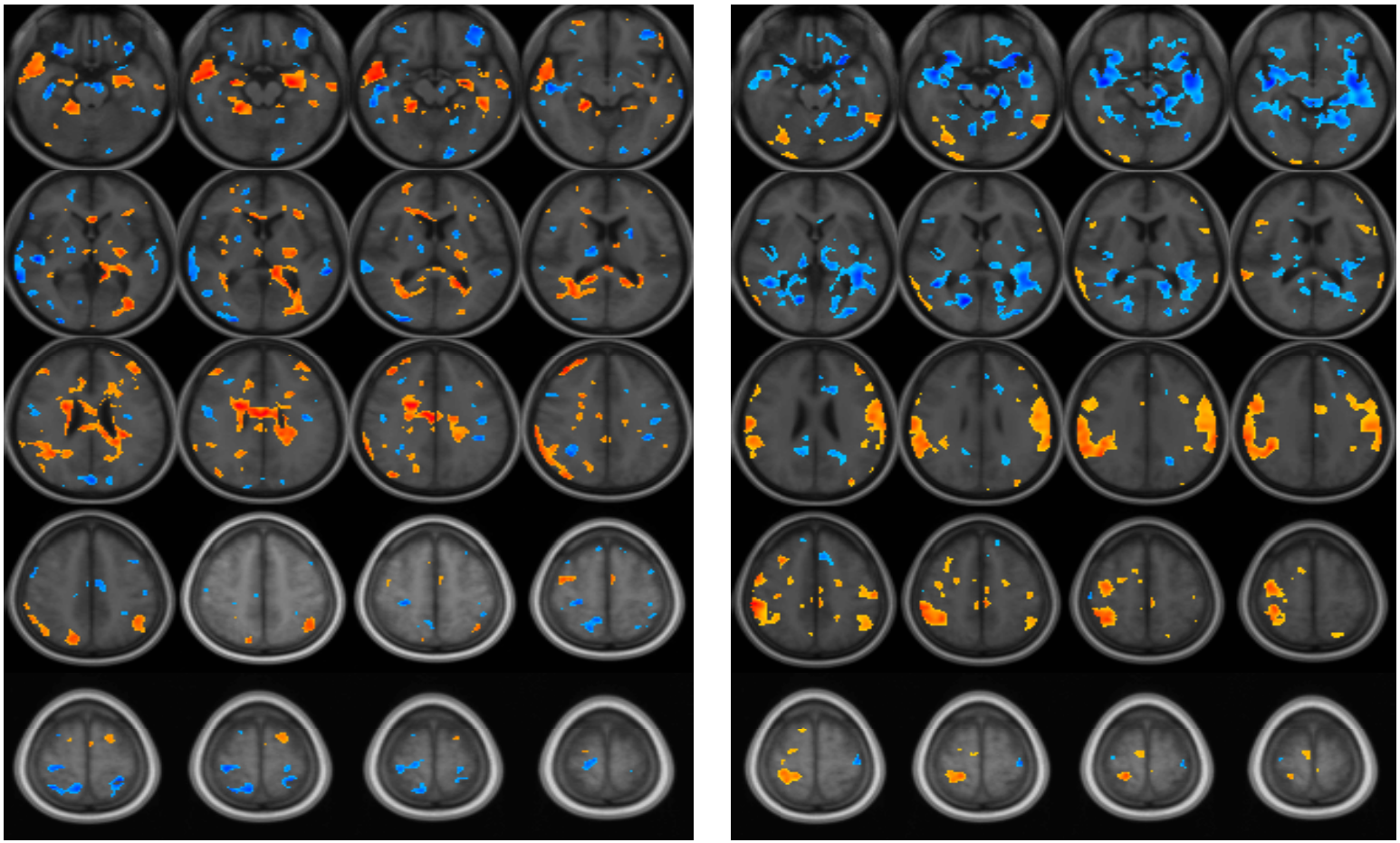
Genes can predict memory accuracy and brain circuitry in schizophrenia



Type AA D1 receptor genotype (on the left) uses more anterior brain circuitry to perform a memory task.

From: E. Tura, J. Fallon, J. Turner, S. Potkin, NeuroReport, 2008

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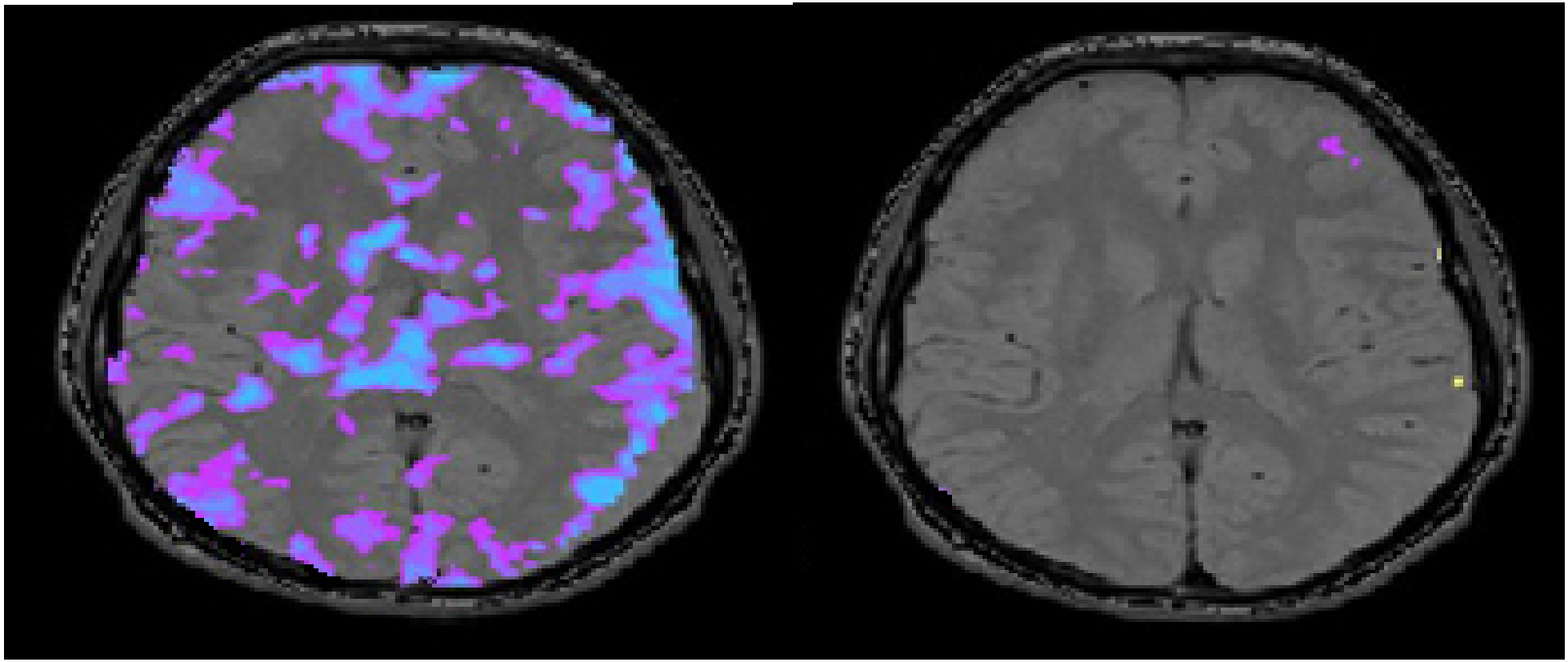
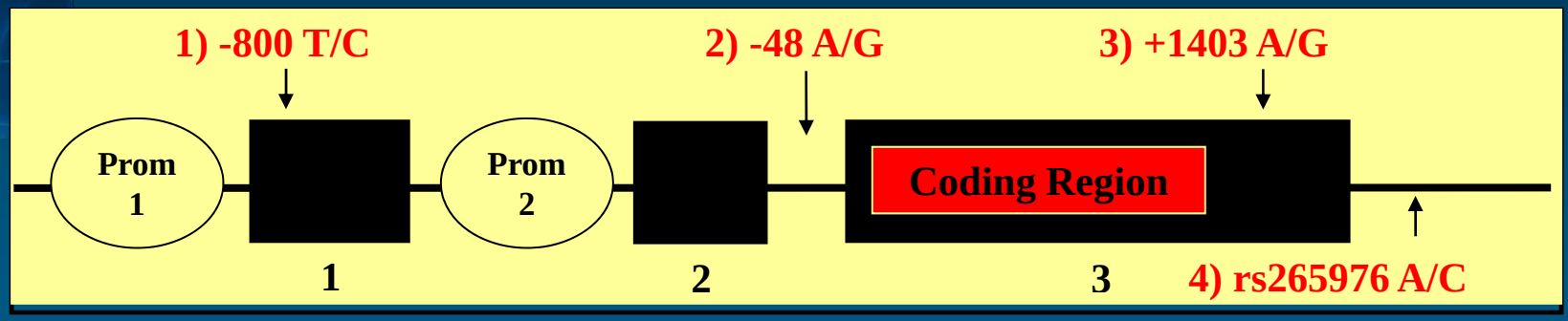
Candidate Gene Approach: Genes can predict clinical response to medication



The AA but not the GG and GA D1 receptor genotype (left) respond to clozapine clinically and metabolically

From: Potkin et al 2003

DRD1 Polymorphisms in Clozapine Response (N=234)



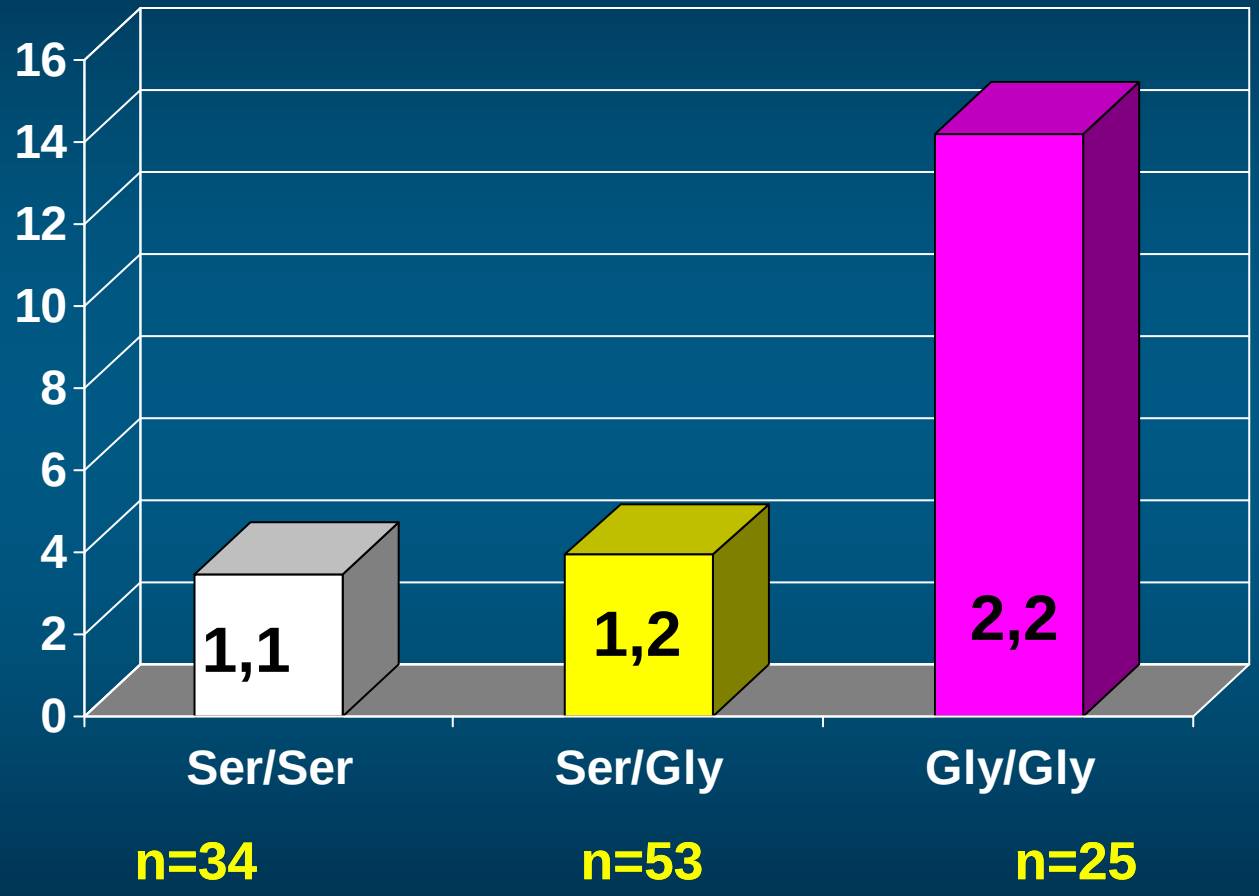
Ethnicity	Global P Value	Haplotype	Responder: n (Est. Freq.)	Non-Responder: n (Est. Freq.)	P Value
Caucasian	0.616	1-2-1-2	0.9 (0.01)	5.7 (0.02)	**0.016**
African-American	0.189	1-2-2-2	3.0 (0.06)	0.0 (0.00)	**0.042**

-48 G allele over represented in the non responders

"2" is the G allele; molecular mechanism unknown

Kenedy J et al ASSOCIATION STUDY OF FOUR DOPAMINE D1 RECEPTOR GENE POLYMORPHISMS AND CLOZAPINE TREATMENT RESPONSE, 2006

Tardive Dyskinesia after Typical Neuroleptic Treatment by DRD3 Msc I Polymorphism



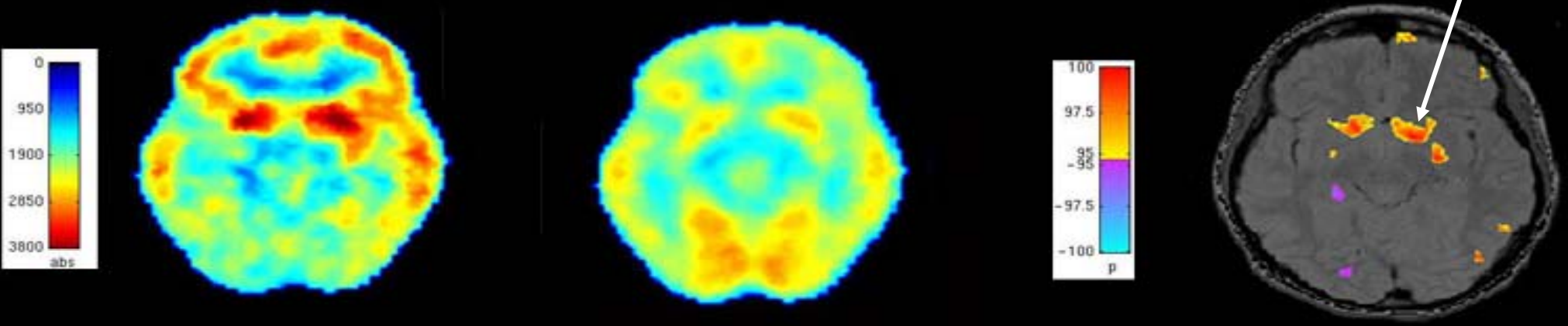
F[2,95] = 8.25, p < 0.0005, Power = 0.568, r-square=0.297

Basile et al 2000

FDG Metabolic Changes With Haloperidol By D_3 Alleles

Oro-facial representation in striatum

Gly-Gly **Other Alleles**



Monte Carlo Threshold

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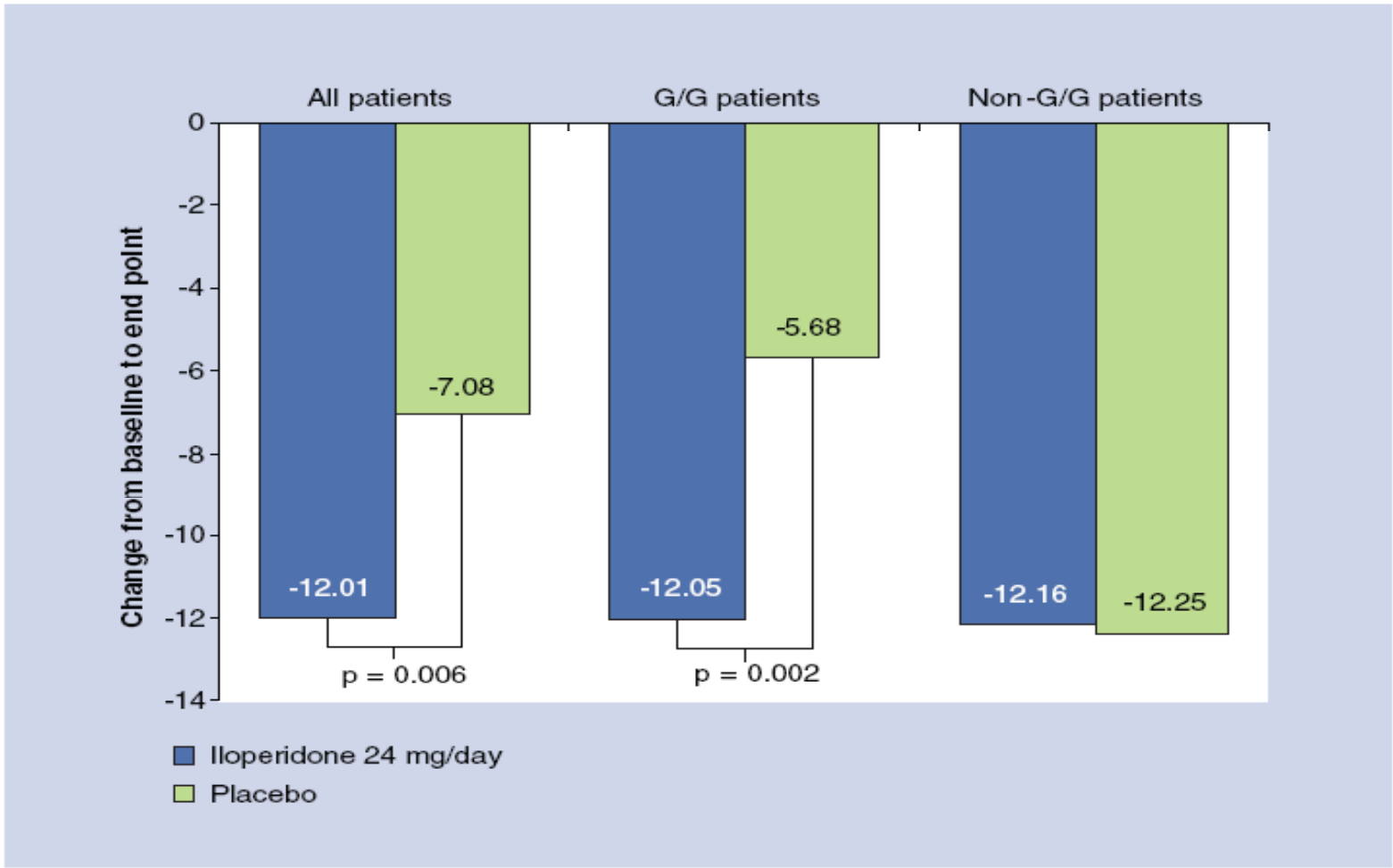
Efficacy Based on CNTF alleles

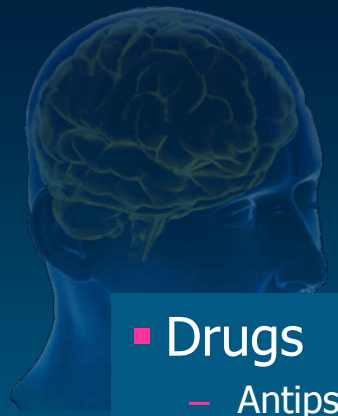
Figure 1. Changes from baseline in PANSS-T scores.*



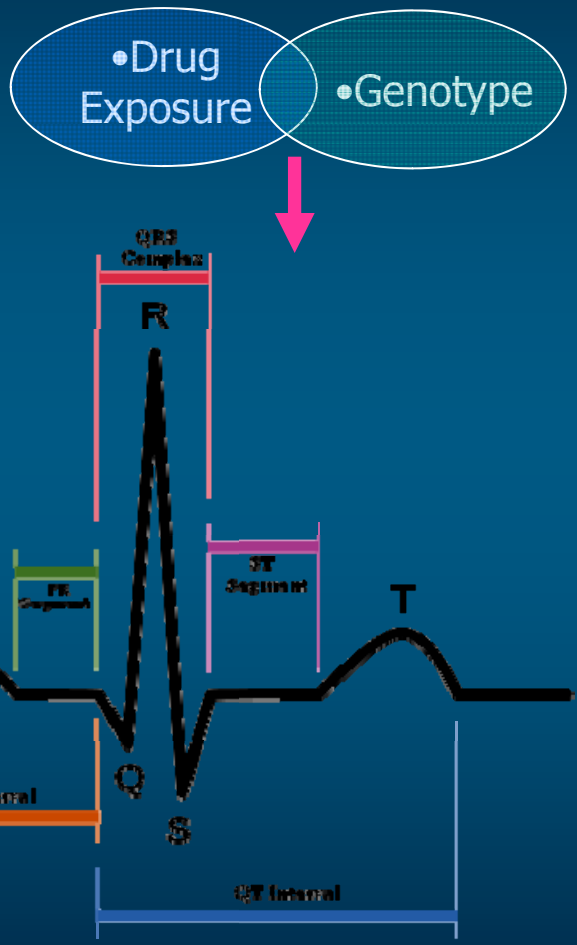
*Negative changes indicate improvement. Means and p-values are from the MMRM modeling.
MMRM: Mixed-effects model repeated measures; PANSS-T: Positive and Negative Syndrome Scale Total.

Lavedan et al Pharmacogenetics 2008

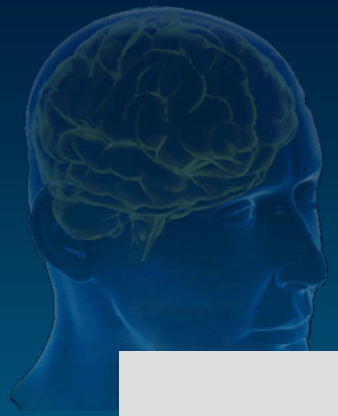
Factors influencing the QT interval



- Drugs
  - Antipsychotics
  - Antihypertensives
  - Antilipidemics
  - β-blockers
  - Antibiotics
  - Anxiolytics
- Age
- Gender
- Race
- Disease



- Genetics
  - LQT1-KCNQ1
  - LQT2-KCNH2 (HERG)
  - LQT3-SCN5A
  - LQT4-ANK2
  - LQT5-KCNE1
  - LQT6-KCNE2
  - LQT7-KCNJ2
  - Others



Study 3101: CYP2D6*4

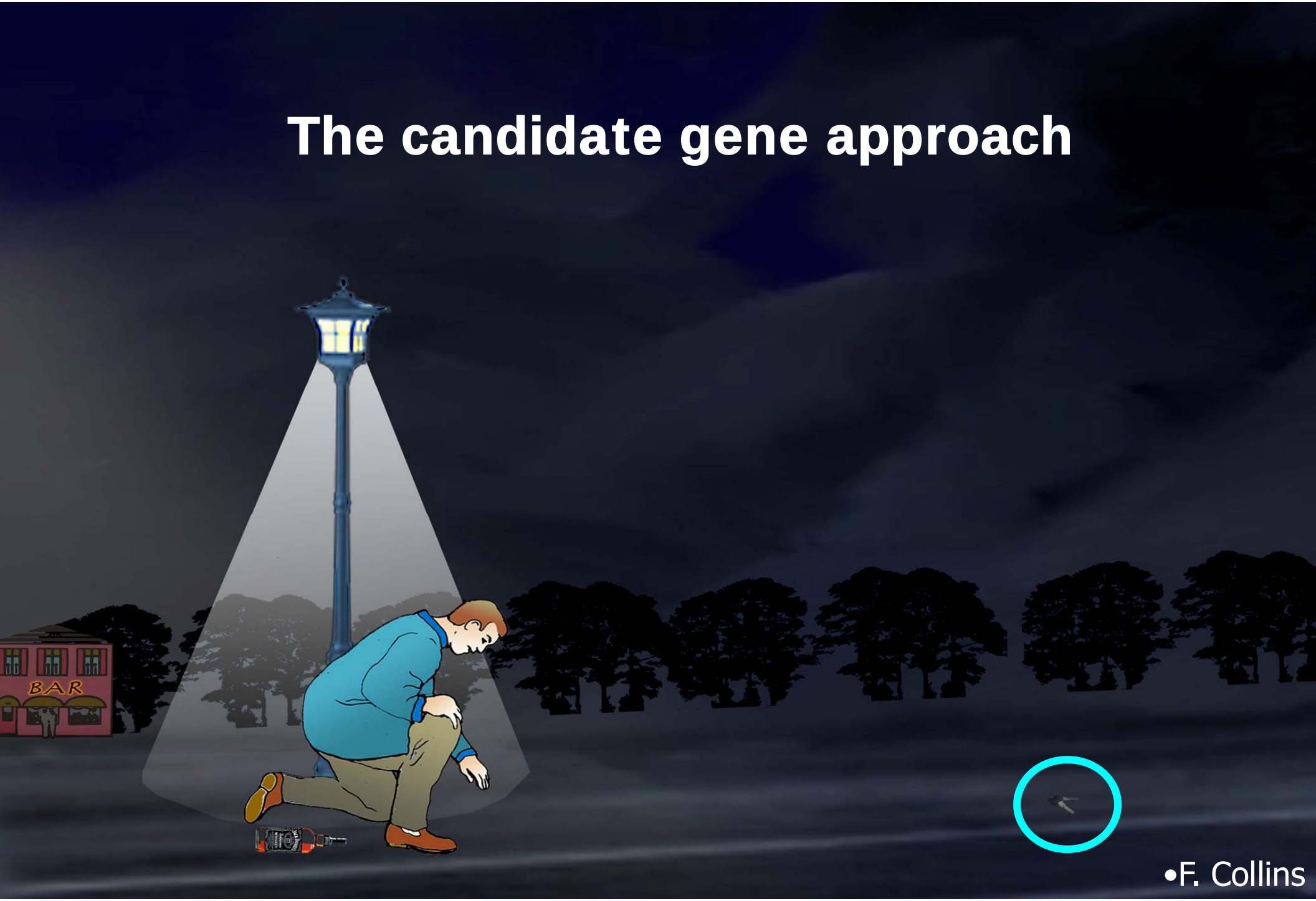
QTcF Change From Baseline (ms)

		Iloperidone			
		G/G (Extensive Metabolizers)	Non-G/G (Poor and Intermediate Metabolizers)	Significance of Difference	All*
Day 14	Mean (range)	**10.4** (-32 to 64)	**15.0** (-21 to 50)	p = 0.008	**11.4** (-32 to 66)
	N	188	56		246

- *Not all patients were available for genotyping

- Other potential genetic markers of QT prolongation were identified in a subsequent WGAS *(Volpi et al. Mol. Psych. 2008)*

The candidate gene approach



•F. Collins

Candidate Gene Approach

- Biological face validity is reassuring but potentially dangerous
- Limited by current knowledge and concepts
- 12 million polymorphism requiring between .5 and 1.5 million SNPs to adequately represent genetic variation

The genome wide association approach

•F. Collins

SNPs Associated With QTc Change

Table 2 Race distribution of genotypes for SNPs significantly associated with change in QT

			Black		*White*		*Others*	
SNP	*Gene*	*Genotypes*[a]	N	*Mean*	N	*Mean*	N	*Mean*
rs993648	*CERKL*	C/T[b]	45	1.79	23	9.19	12	5.66
		Non-C/T[c]	40	17.90	43	15.31	11	27.27
rs3924426	*SLCO3A1*	T/T[c]	52	15.02	63	14.16	20	17.55
		Non-T/T[b]	39	2.19	6	3.13	3	5.67
rs4799915	*BRUNOL4*	C/C[b]	33	3.45	11	5.27	4	−8.43
		Non-C/C[c]	57	12.55	57	14.72	18	19.67
rs4933824	*NRG3*	G/G[c]	40	16.32	63	13.96	21	17.55
		Non-G/G[b]	50	4.28	5	7.60	2	−0.33
rs7142881	*NUBPL*	G/G[b]	55	5.27	17	6.98	7	5.62
		Non-G/G[c]	35	16.28	49	15.83	15	20.62
rs17054392	*PALLD*	C/T[b]	26	−1.09	1	−1.53	3	3.00
		Non-C/T[c]	65	13.77	68	13.42	20	17.95

Abbreviation: SNP, single nucleotide polymorphism.
SNPs are identified by their unique dbSNP number reported at NCBI dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP/index.html)[17] and are listed in ascending order of dbSNP number.
The gene name corresponds to the NCBI official symbol.
Number of patients (*N*) and mean change in QT (in ms; Mean) are shown per race.
[a]Genotypes correspond to the + strand of the DNA as reported at NCBI dbSNP.
[b]Genotype classes associated with the lowest mean increased QT.
[c]Genotype classes associated with the highest mean increased QT.

Cost Benefit

- If QTc risk alleles are indeed predictive would the 18,000 subject Zodiac study have been required?
- Should QTc alleles or GWAS be part of Phase 3: is it cost effective?
- Is there a danger of shrinking of the population-based blockbuster drug model to a narrower targeted therapy subpopulation?
- Are narrow regulatory approvals inevitable?

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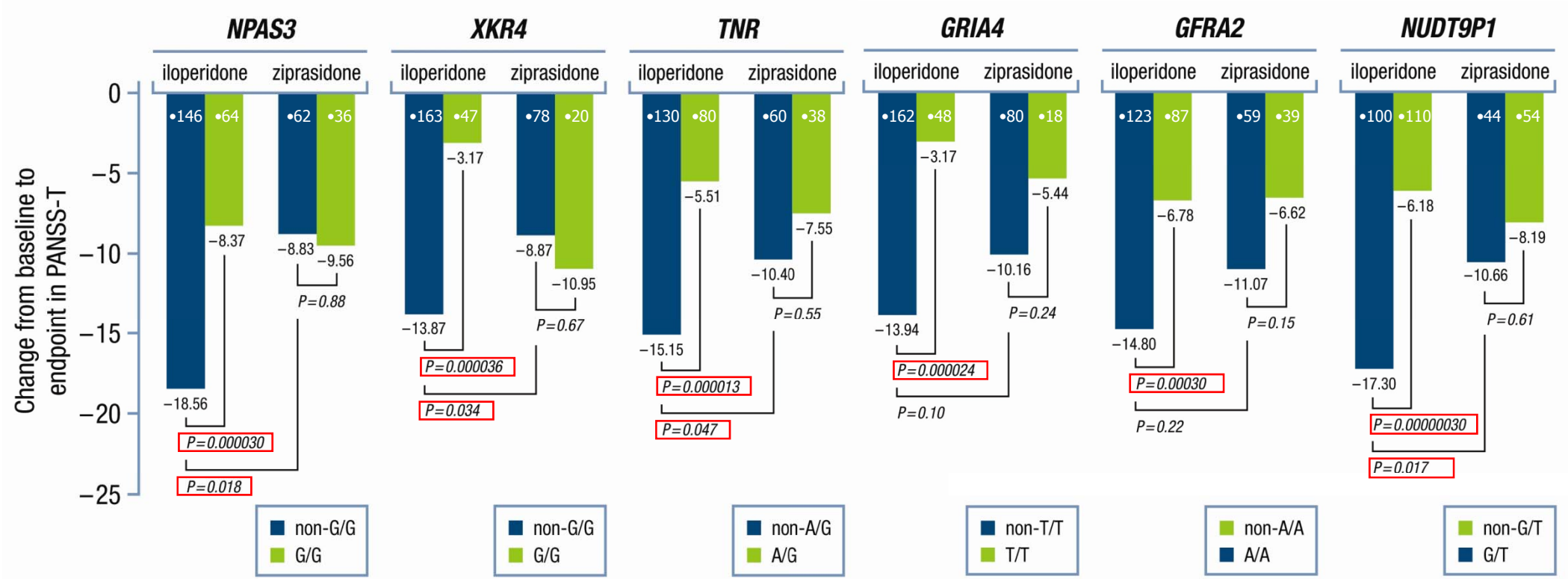
6 SNPs associated with iloperidone efficacy

SNP	Gene	Function
rs11851892	*NPAS3*	Transcription factor expressed in hippocampus, thalamus and cortex. Mutated in a family with schizophrenia. Risk and protective haplotypes detected in schizophrenia and bipolar disorder
rs9643483	*XKR4*	Codes for a protein related to the XK protein, a putative membrane transporter
rs875326	*TNR*	Tenascin R is an extracellular matrix protein expressed primarily in the CNS and localized around motor neurons and on motor axons in the spinal cord, cerebellum, and hippocampus. Exerts beneficial effects on tissue regeneration in a mouse model of neurodegenerative disease
rs2513265	*GRIA4*	APMA 4: Codes for an L-glutamate–gated ion channel that is involved in fast excitatory neurotransmission. Some *GRIA4* haplotypes have been associated with schizophrenia in Japan
rs7837682	*GFRA2*	The GFRA2 protein is a receptor for the glial cell-line derived neurotrophic factor (GDNF) and neurturin
rs4528226	*NUDT9P1 HTR7*	Between pseudogene and the serotonin receptor 7 gene. iloperidone has high affinity for the 5-HT_7 receptor

GWAS done in Phase 3 trial; n= 407

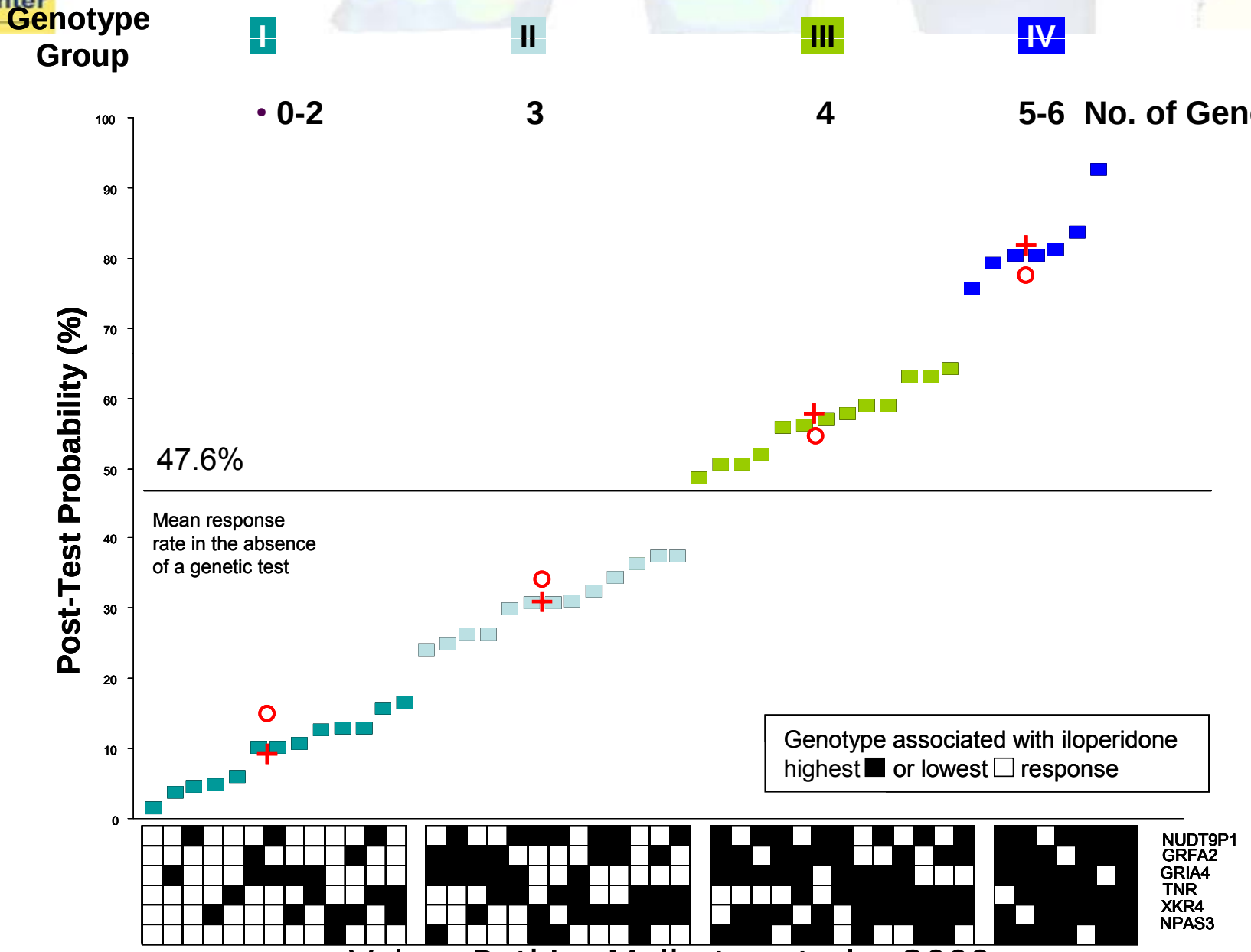
•*Adapted from Lavedan C, et al. Mol Psychiatry. 2008*

Effect of individual SNPs on Efficacy



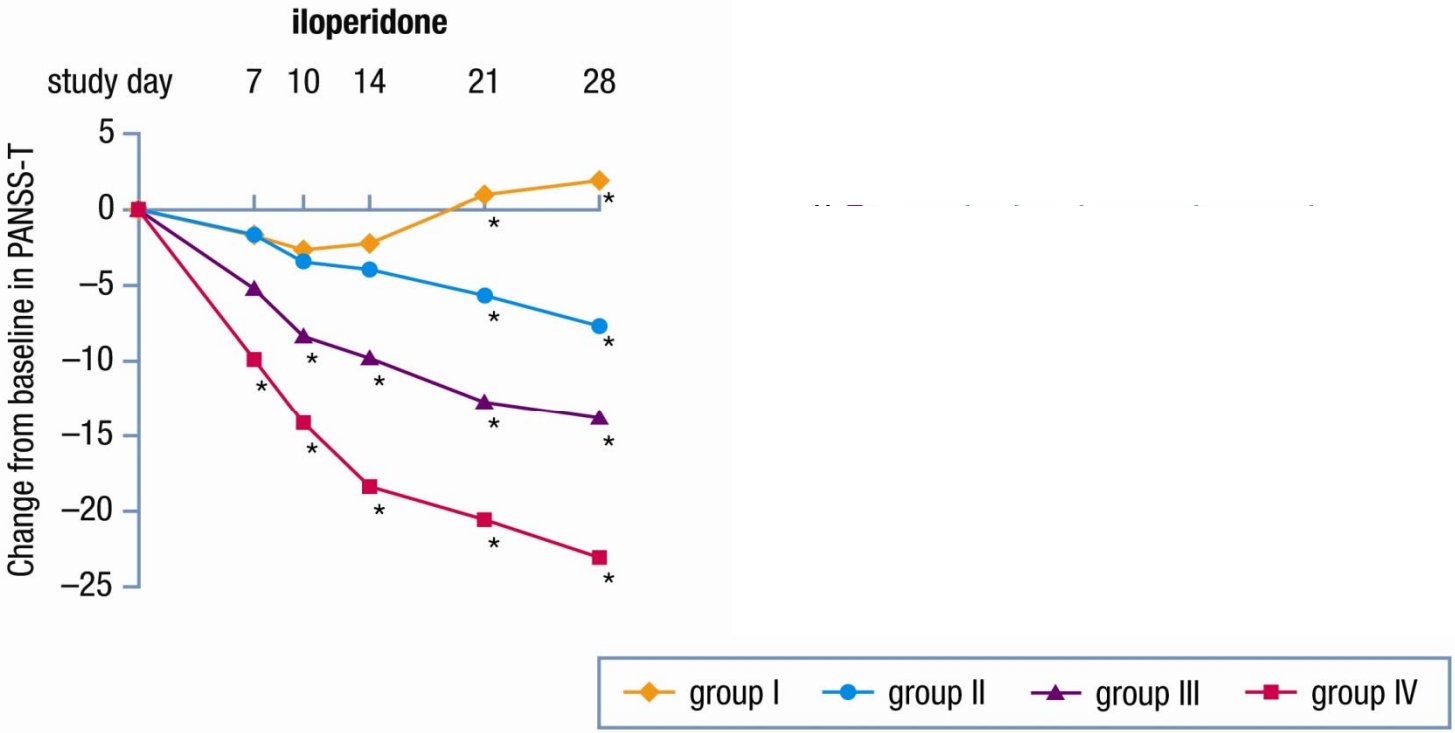
•*Adapted from Volpi et al., in press*

Clinical Response By Genotype



•Volpe, Potkin, Malhotra et al., 2009

Time course of treatment response per genotype

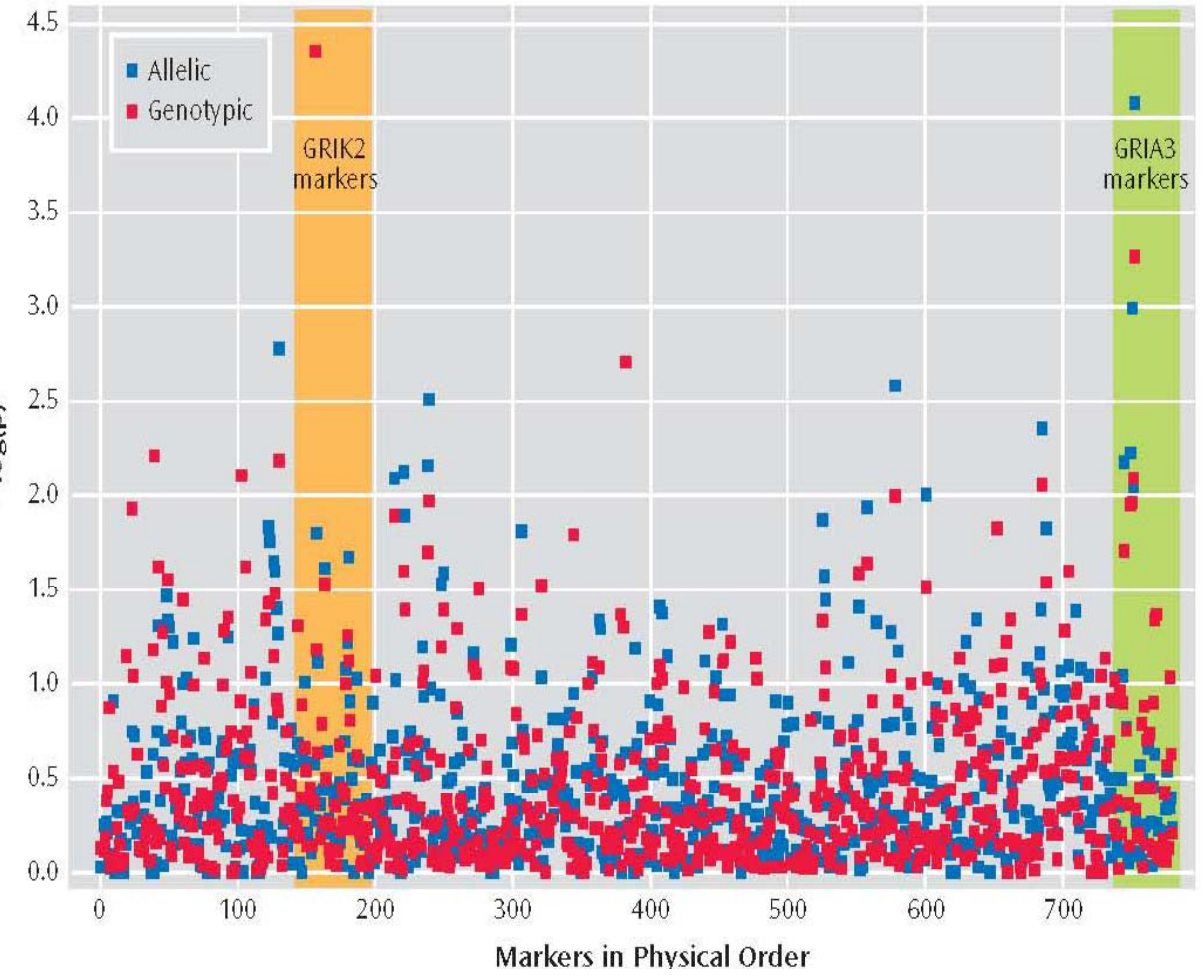


- ** p<0.05 for all pairwise comparisons with the other 3 genotype groups*

If remove Group 1 does it bias the sample?

- *Adapted from Volpi et al., in press*

Genetic Markers of Suicidal Ideation Emerging During Citalopram Treatment of Major Depression



		CEU	AA	Asia
GRIK2 kainate	C	.18	.04	
rs2518224	A	.82	.95	
AMPA3	G	.25	.41	.43
rs4825476	A	.75	.59	.57

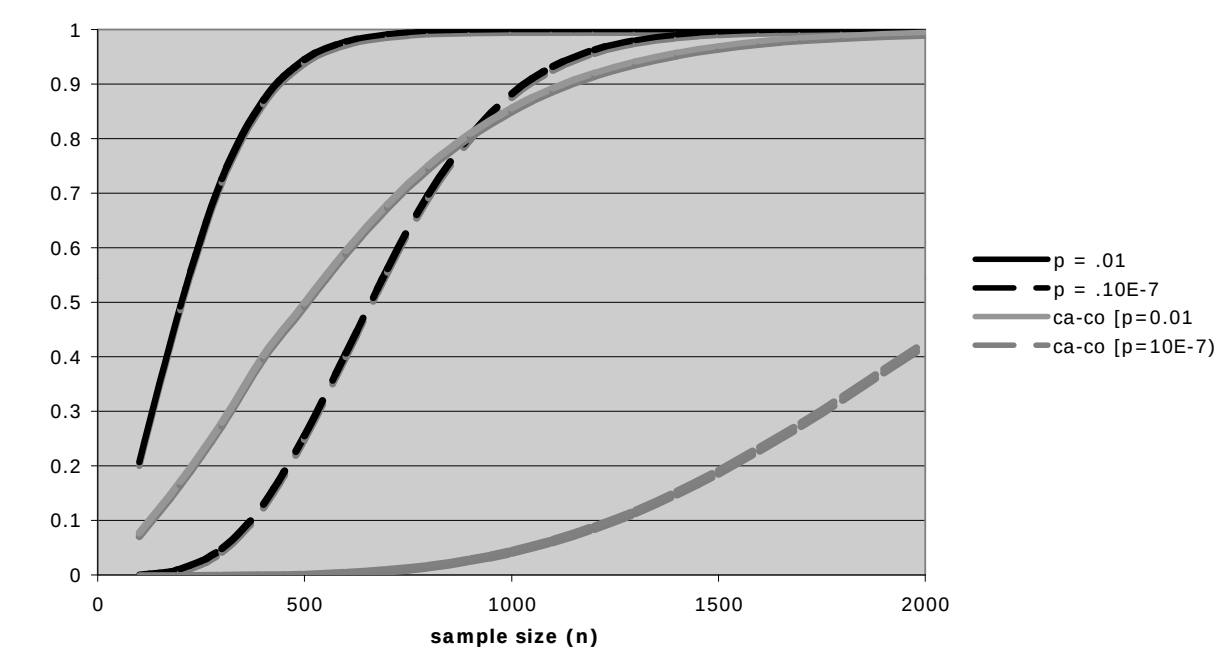
n=1,915; Genotyped for SNPs in 68 candidate genes

Laje et al. Am J Psychiatry 2007; 164:1530–1538

QTs increase power and reduce needed sample sizes

Power distribution curves for QT analysis contrasted with a case-control design:

1. $p < .01$ and 10^{-7} (OR = 1.5)
2. 10% percentage variance explained for the QT
3. QT MAF of 10%
4. marker SNP MAF at 20



Compared to QT the case-control curves are shifted to the right indicating that much larger sample sizes are required to reach the same power.

Potkin et al ., Cognitive Neuropsychiatry, 2009 , 14(4):391-418

Hippocampal Atrophy as a Quantitative Trait in a Genome-Wide Association Study Identifying Novel Susceptibility Genes for Alzheimer's Disease

UC Irvine: S. Potkin, G Guffanti, A Lakatos, JA Turner, F Kruggel, JH Fallon,
Other Contributors: AJ Saykin, A Orro, S Lupoli, E Salvi, M Weiner, F Macciardi, ADNI

Chromosome	Gene Context	SNP	Coordinate(Build 36.3)	Genomic context - Distance to gene	p-value
1	AL157404.18 - S100A5	rs4845552	151746622	7 Kbp from AL157404.18	6.23×10^{-6}
5	AC026790.5	rs682748	17201911	9 Kbp from the upstram of AC026790.5	8.14×10^{-6}
5	AC022418.5	rs7727656	25796436	desert region	8.27×10^{-6}
5	AC104108.3 -SCAMP1 - LHFPL2	rs6881634	77666610	14 Kbp from AC104108.3	1.93×10^{-6}
5	ARSB	rs337847	78295644	intron 3	6.71×10^{-6}
5	EFNA5	rs10074258	107010459	intron1	2.15×10^{-7}
5	EFNA5	rs12654281	107068341	30 Kbp from 5'UTR of EFNA5	3.72×10^{-7}
5	EFNA 5	rs12657273	107074597	36 Kbp from 5'UTR of EFNA5	8.92×10^{-6}
7	AC096553.4	rs9918508	9505804	desert region	8.49×10^{-6}
7	IKZF1 - AC020743.7	rs2124799	50240560	desert region - 75 Kbp from IKFZ1	8.54×10^{-6}
7	IKZF1 - AC020743.7	rs10276619	50283898	desert region - 31 Kbp from IKFZ1	2.94×10^{-6}
7	MAGI2	rs11525066	78013913	intron 3	2.85×10^{-6}
8	MAL2	rs1364705	120293987	intron 2	8.92×10^{-6}
9	PRUNE2	rs10781380	78597964	intron 6	7.13×10^{-7}
9	RP11-232A1.1	rs10867752	83204857	8 Kbp from the upstream of RP11-232A1.1	3.08×10^{-6}
11	ETS1	rs6590322	127711620	desert region	9.37×10^{-6}
12	ARID2 - SFRS2IP	rs1373549	44772105	100 Kbp downstream SFRS2IP	7.80×10^{-6}
12	CAND1	rs1082714	65915098	34 Kbp from 5'UTR of CAND1	4.93×10^{-6}
13	RP11-506F17.1	rs9301535	85984283	desert region	7.90×10^{-6}
13	RP11-506F17.1	rs4773460	86040858	desert region	1.93×10^{-6}
14	FRMD6 - AL079307.7	rs11626056	51303026	upstream region of AL079307.7	1.18×10^{-6}
20	C20orf132	rs8115854	35199751	exon 11 - non-synonymous coding	2.09×10^{-6}
20	RPN2	rs6031882	35243197	intron 1	6.20×10^{-6}
20	ZBP1	rs2073145	55624040	exon 2 - non-synonymous coding; splice site	2.13×10^{-6}
21	FDPSP	rs1888414	20699601	desert region - 16 Kbp from FDPSP	2.41×10^{-7}

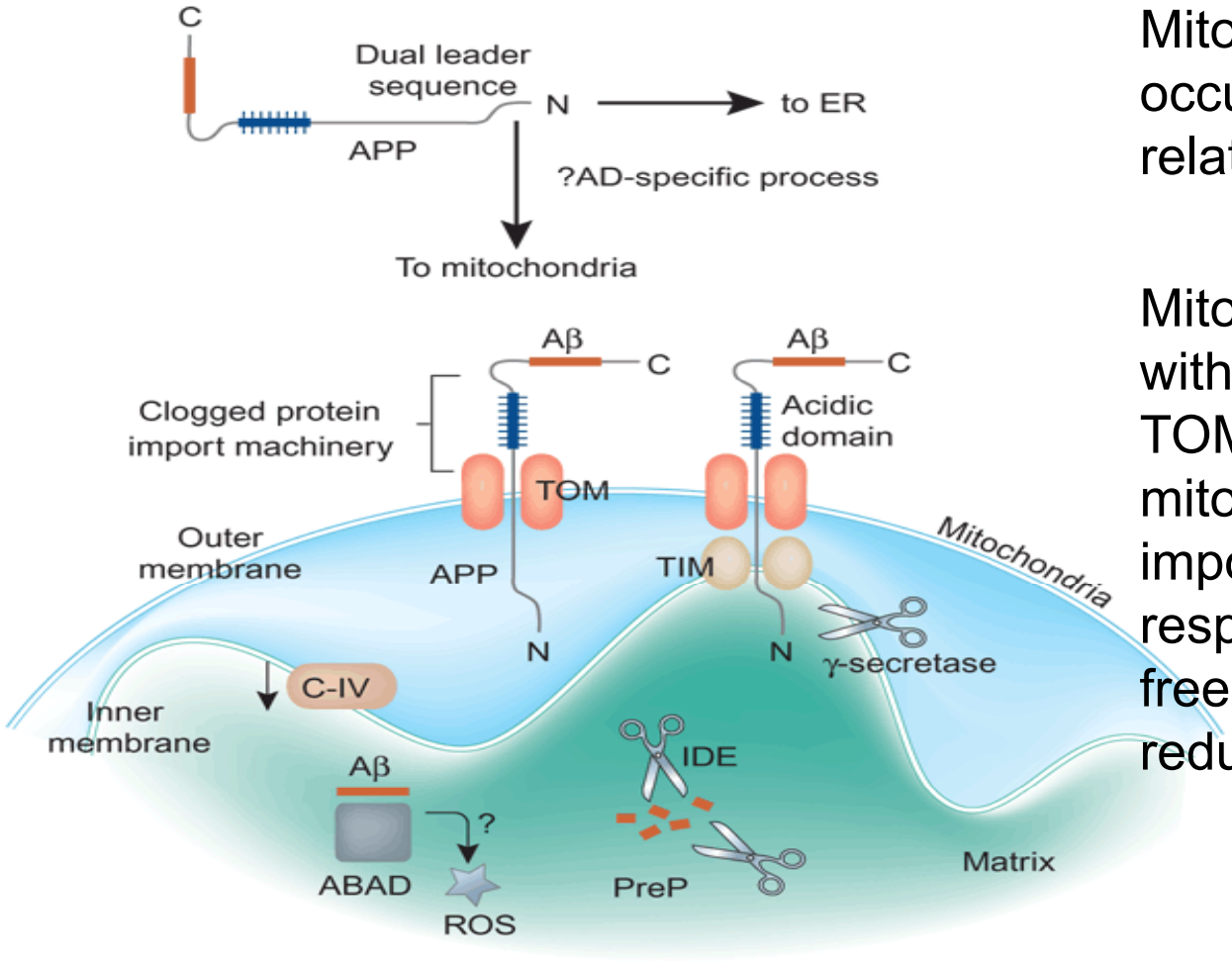
•Adapted from: Potkin, Guffanti, et al. (2009) PLoS ONE 4(8): e6501

- The **case-control** analysis identified **APOE** and a new risk gene, **TOMM40**, at a genome-wide significance level of p-value ≤ 10^{-6}

- The **quantitative trait** analysis identified **21 genes or chromosomal areas** with at least one SNP with a p-value ≤ 10^{-6}.

- Apoptosis, cell cycle impairment and the alteration of protein folding and degradation through ubiquination are among the candidate pathophysiological mechanisms

Mitochondrial Dysfunction



Mitochondrial localization of APP occurs only in AD subjects and is related to disease severity.

Mitochondrial APP forms complexes with the protein importation with TOMM40 (translocases of the outer mitochondrial membranes) and clogs importation with resultant decreased respiratory chain enzymes, increased free radical generation and impaired reducing capacity.

•*After Nature Medicine* - **12**, 1241 - 1243 (2006)
doi:10.1038/nm1106-1241 **Alzheimer's APP mangles mitochondria**
•Michael T Lin & M Flint Beal

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The Future Is Here

Probabilities of medication response and development of side-effects

	Efficacy	Negative	Cognitive	DM	Weight	Suicide
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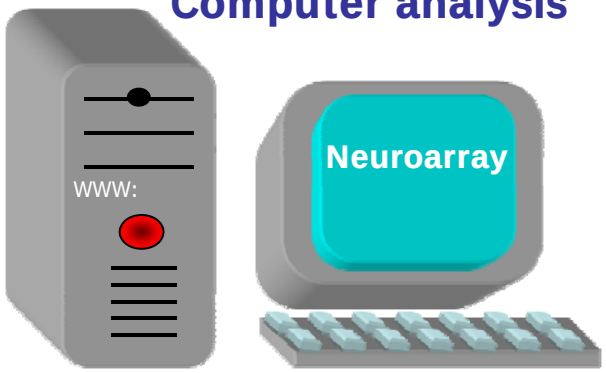
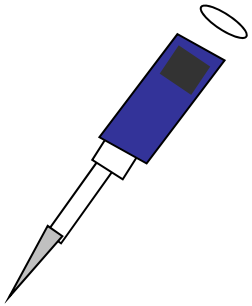
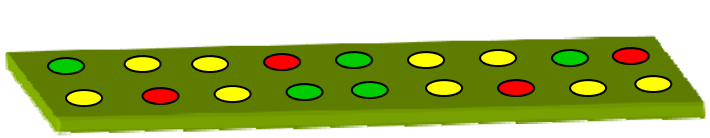
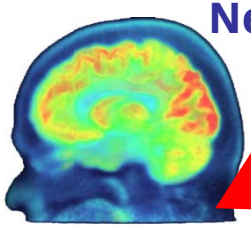




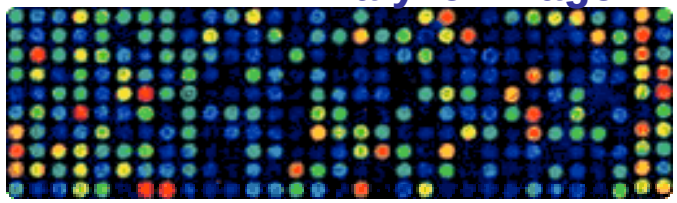
Blood sample in physician's office



Gene Chip



Neuroimaging



Analyze Image

after Potkin et al 2002

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Reality Examples

No one medication owns the market

Drugs are not effective in all subjects

Although drugs cause serious side-effects in only a few subjects the consequences can be dramatic

- Aganulocytosis with clozapine
- Suicidality on antidepressants
- Behavioral problems of elderly

FDA precedent using retrospective data:

Carbamazepine and HLA-B*1502 (~14% in Asians)

Is prospective data required?

FDA narrows drug label usage - August 2009

Cancer treatments limited to specific gene variants.

- The US Food and Drug Administration (FDA) has altered the usage labels on two cancer drugs, Erbitux and Vectibix, on the basis of a re-evaluation of clinical data.

- The Oncologic Drugs Advisory Committee recommended that, for patients with advanced-stage colorectal cancer — both drugs should be prescribed only to individuals with a certain gene variant.

- To reach the decision, the agency reviewed seven randomized clinical trials, all of which showed that only the 60% or so of patients whose tumours harbour the non-mutated or 'wild-type' *form of K-RAS gene responded* positively to the drugs.

What Pharma most fears?

Need for replication?

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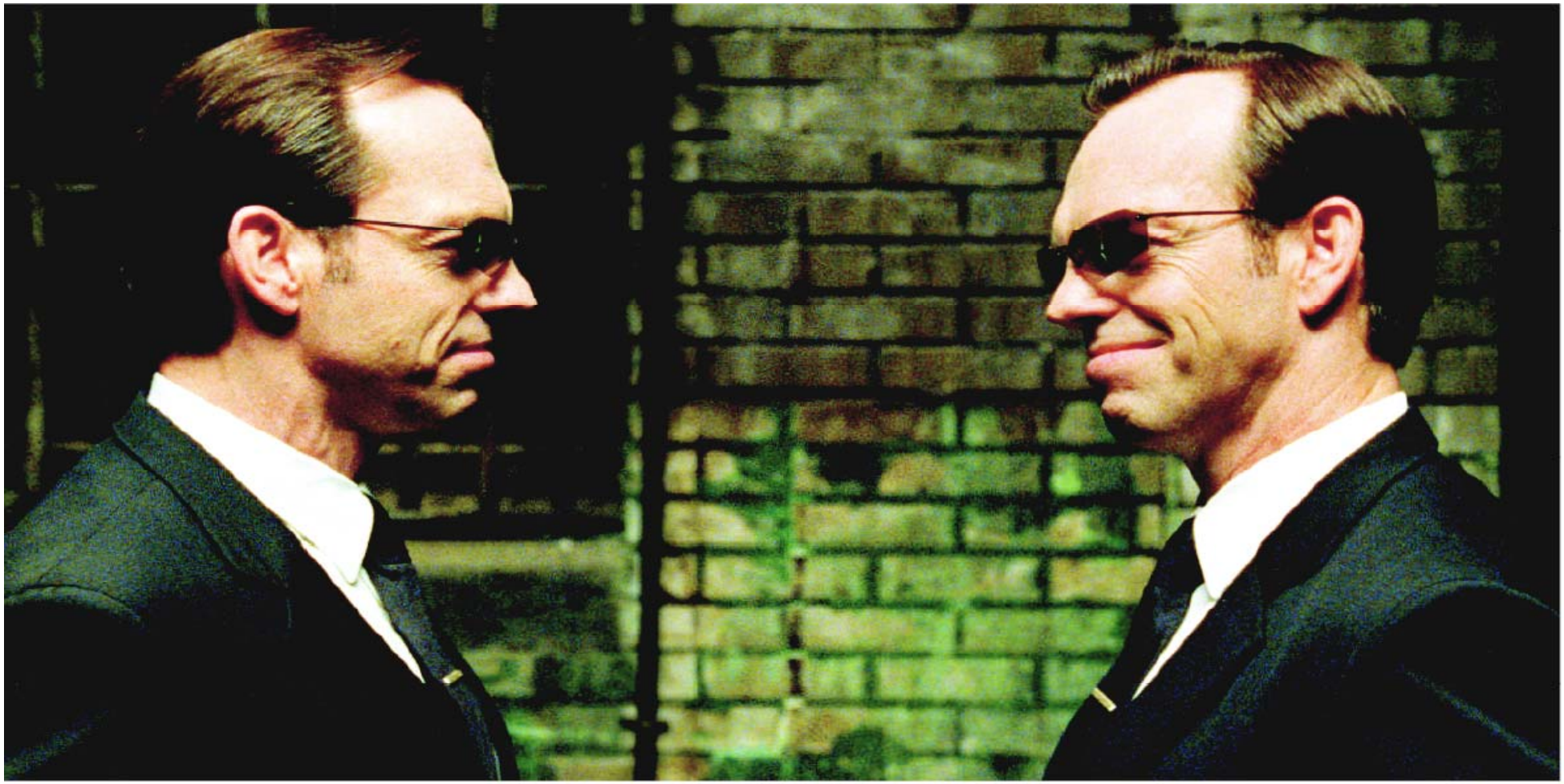
nature, 27 July 2006



THE TROUBLE WITH REPLICATION

What is a true replication?

Replication Outcome	Explanation
Association to same trait, but different gene	Genetic heterogeneity
Association to same trait, same gene, different alleles (or haplotypes)	Allelic heterogeneity
Association to same trait, same gene, same allele – but in opposite direction (protective ←→ disease)	Allelic heterogeneity/popln differences
Association to different, but correlated phenotype(s)	Phenotypic heterogeneity
No association at all	Sample size too small

After L. Cardon

Defining Success

Replication –SNP direction, SNP, haplotype, gene, or pathway

- Need to define objective criteria for what is/is not a replication *in advance*

Stratification dangers - why trials must be ethnically and perhaps geographically distributed

Predictive Value of Imaging

- Changes in function may predate changes in structure in diagnosis of AD v non AD. For example decreases in metabolism but not volume can be seen before memory changes. APO-E.
- If clinical dx of AD APO 4 increased prediction from 90 to 94%; absence of E4 increase negative predictive value from 645 to 72%.
- SPECT if 30 to 50% sure of dementia SPECT increase probability of AD by 30% but negative decrease likehood of absence of AD by only 10%; PET 93% sensitivity and 63% specificity.
- 284 dementia patients (138 autopsy confirmed diagnosis) Sensitivity 93%; specificity 76%
- Negative PET scan indicated chance of cognitive progression <20% over 3 years (Silverman 2001)

Personalized Medicine: Relapse Avoidance

Trial-and-error dosing leads to less effective response, more relapses & hospitalizations

If same payer cost savings clear & feasible

Warfarin Dosing example:

Difficult to dose due to variation; effective doses range from 0.5mg to 60 mg/day

From Warfarin Label

- **CYP2C9** Increased bleeding risk for patients carrying either CYP2C9*2 or CYP2C9*3 alleles.

  (Mean dose 17% and 37% less than CYP2C9*1)
- **Protein C or its cofactor, protein S** associated with tissue necrosis but not all patients develop necrosis, and TN occurs in patients without these deficiencies.
- **Vitamin K epoxide reductase (VKOR) Variant-** Certain SNPs in VKORC1 gene (-1639G) associated with lower dose requirements.
  - African Americans are relatively resistant to warfarin (higher proportion group B haplotypes), while Asian Americans are generally more sensitive (higher proportion group A haplotypes).

From FDA Regarding Warfarin Label

- "About 55% of the variability in warfarin dose could be explained by the combination of VKORC 1 and CYP2C9 genotypes, age, height, body weight, interacting drugs, and indication for warfarin therapy in Caucasian patients. Similar observations have been reported in Asian patients."

Pharmacogenomic information is in about 10% of labels for drugs approved by the FDA

Adverse Event Avoidance for Warfarin Financial Consequences

Difficult to dose because effective doses range from 0.5mg to 60 mg/day.

Trial-and-error dosing leads to under-dosing with strokes, over-dosing to fatal hemorrhages.

Genetic testing to guide dosing could avoid 85,000 serious hemorrhages and 17,000 strokes annually in U.S.

Costs: hemorrhage $13,500; stroke is $39,500.

Annual savings - $1.1 billion to U.S. health care.

Adverse Event Avoidance

Carbamazepine & Lamotrigine can rarely cause Steven Johnsons/toxic epidermal necrolysis

SJ/TEN association with HLA-B1502 lead to FDA label change for Asians (15% v<1%)

No association found in Europeans with SJ

No warning with lamotrigine

May be cross-reactivity with oxacarbamazine

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Questions?

Could one enrich subject selection to remove exaggerated placebo subjects?

- Placebo response is very costly in drug development
- Phase 2 or 3? Regulatory implications? Narrow approvals?

Failure to predict efficacy and side-effects risk has costs

- Premature stopping when titration, side –effects, delayed
- Rare side-effects can result in costly damages or regulatory consequences

- What is the risk-benefit trade off?

Should Pharma pool genotype data? FDA requirement?

Personalized Medicine Cautions

- Projections even when high are only probabilities and while they work for groups may disadvantage individuals
- Mandates by payors can dramatically effect the profitability of personalized medicine
- Can render current therapies obsolete or create additional add on costs
- Personalized medicine can reduce R&D cycle time
- From blockbusters to more therapies – smaller markets
- Late adaptors may find their treatments obsolete

Sixth International Imaging Genetics Conference

Beckman Center of the National Academy of Sciences
UC Irvine, CA
January 18-19, 2010

•Visit www.imaginggenetics.uci.edu

for registration and abstract submission

•When: January 18-19, 2010

Location: Beckman Center of the National Academy of Sciences, Irvine, CA
Co-Chairs: Steven G. Potkin and Daniel R. Weinberger

•**What:** The conference will feature state-of-the-art presentations on neuroimaging, genetics, and statistical issues as they relate to the field of Imaging Genetics

❖**Educational Workshops** in Imaging Genetics on Sunday January 17th

❖**Poster presentations** on current research in the field of Imaging Genetics- Abstract submissions will be accepted starting in May of 2009

❖**Themes for 2010:**

•Methodology, Systems Biology, and Studies using Imaging Genetics

•**Vince Calhoun, UNM**: "Multivariate analyses and simulations of multimodal imaging genetic datasets"

•**Guia Guffanti, Univ. of Milan**: "Statistical analysis of interaction terms in GWAS: Permutation test methods"

•**J.B. Poline, Inst. of Biomed. Imaging, France**: "Large scale imaging genetics informatics and analyses in Europe"

•**Arthur Lander, UCI**: "From mouse to man: the glypican model and methods"

•**Peter Kochunov, Univ. of Texas**: "Genetics of cerebral aging as seen from the neuroimaging perspective"

•**Daniel R Weinberger NIMH**

•**Alessandro Bertolino , Bari Italy**