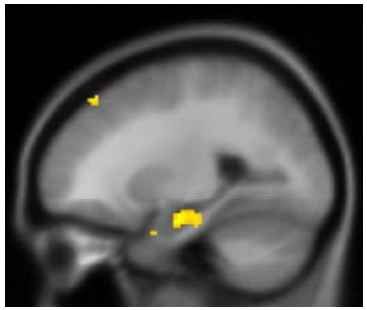
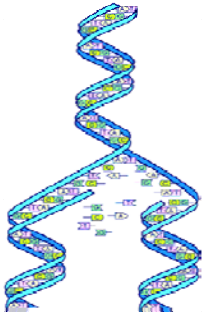
Personalizing human memory capacity: What is feasible, what is desirable





Prof. Andreas Papassotiropoulos, M.D.

Division of Molecular Neuroscience

Faculty of Psychology and University Psychiatric Clinics

Life Sciences Training Facility, Biozentrum

University of Basel, Switzerland

Academia Engelberg, Personalized Genomics/Medicine, September 14-16 2011

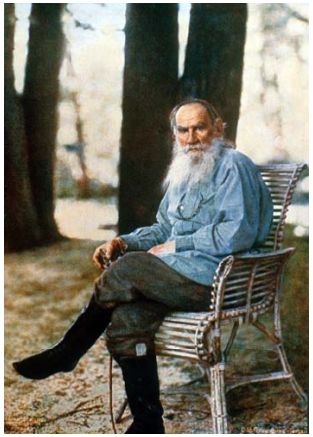
Bullet points

- Genetics of complex human phenotypes: A tool to understand biology
- Genome-wide association studies revolutionize our knowledge on complex traits relevant to neuropsychiatric diseases
- The use of human genetic information will lead to improved characterization of human complex traits
- The combination of genetics with other relevant sources of information (e.g. fMRI, PET) will increase biological knowledge

Quote on personalized medicine

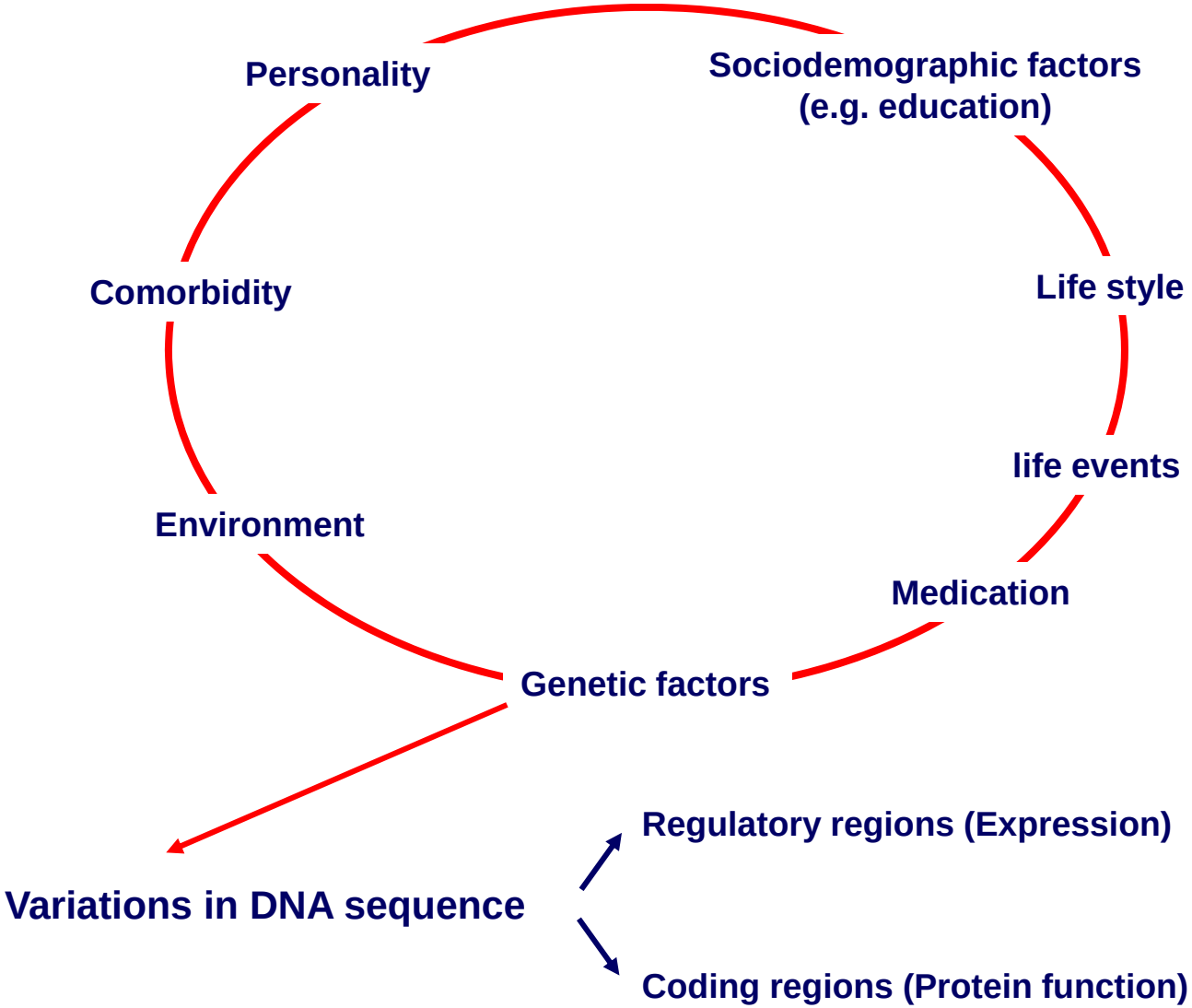
"Doctors came to see her singly and in consultation, talked much in French, German, and Latin, blamed one another, and prescribed a great variety of medicines for all the diseases known to them, but the simple idea never occurred to any of them that they could not know the disease she was suffering from,

as no disease suffered by a live man can be known, for every living person has his own peculiarities and always his own peculiar, personal, novel, complicated disease, unknown to medicine…."

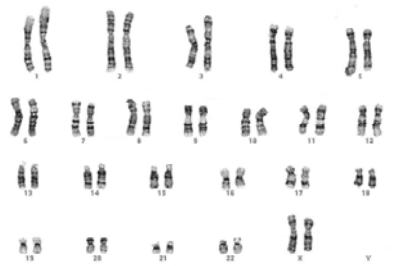


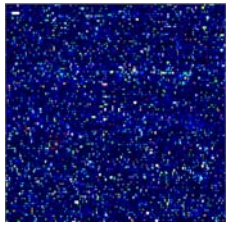
War and Peace
1869
Leo Tolstoy

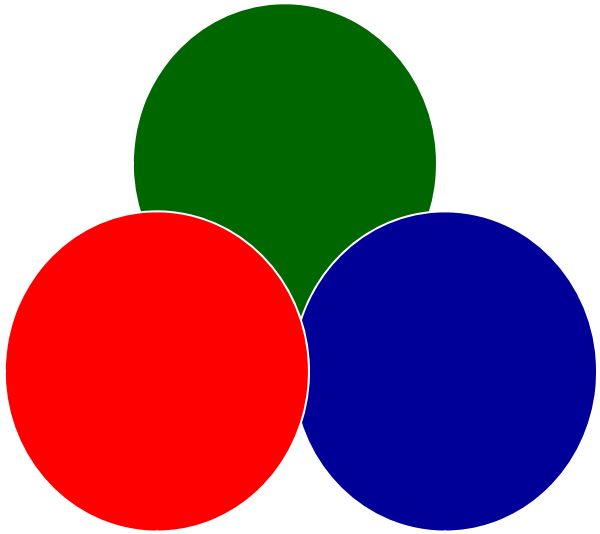
Multifactorial model



Personalized genomics?





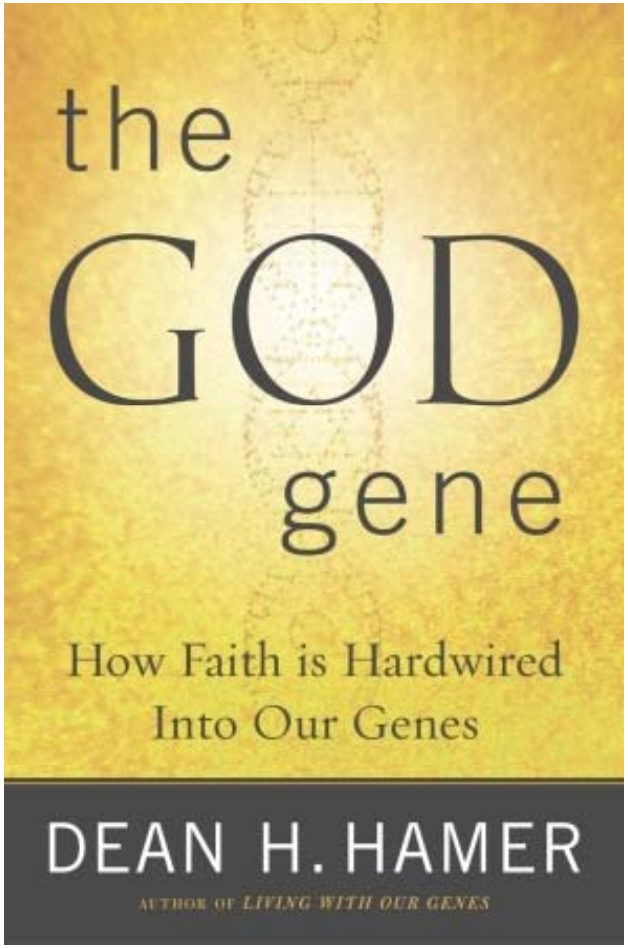


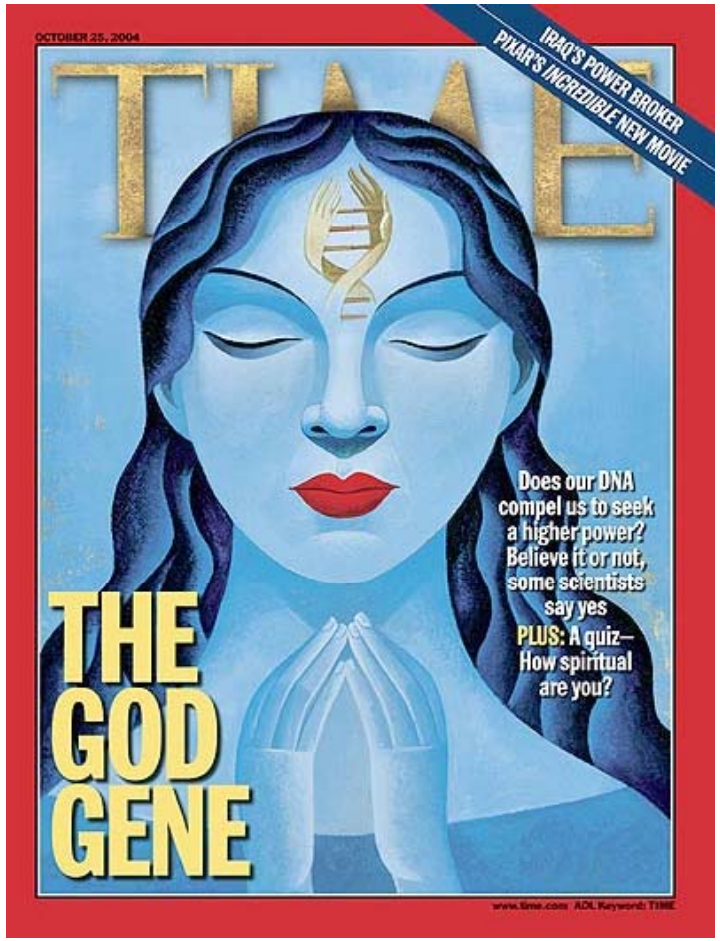
Prediction?

Diagnosis?

Pharmacogenomics?

Importance of the phenotype



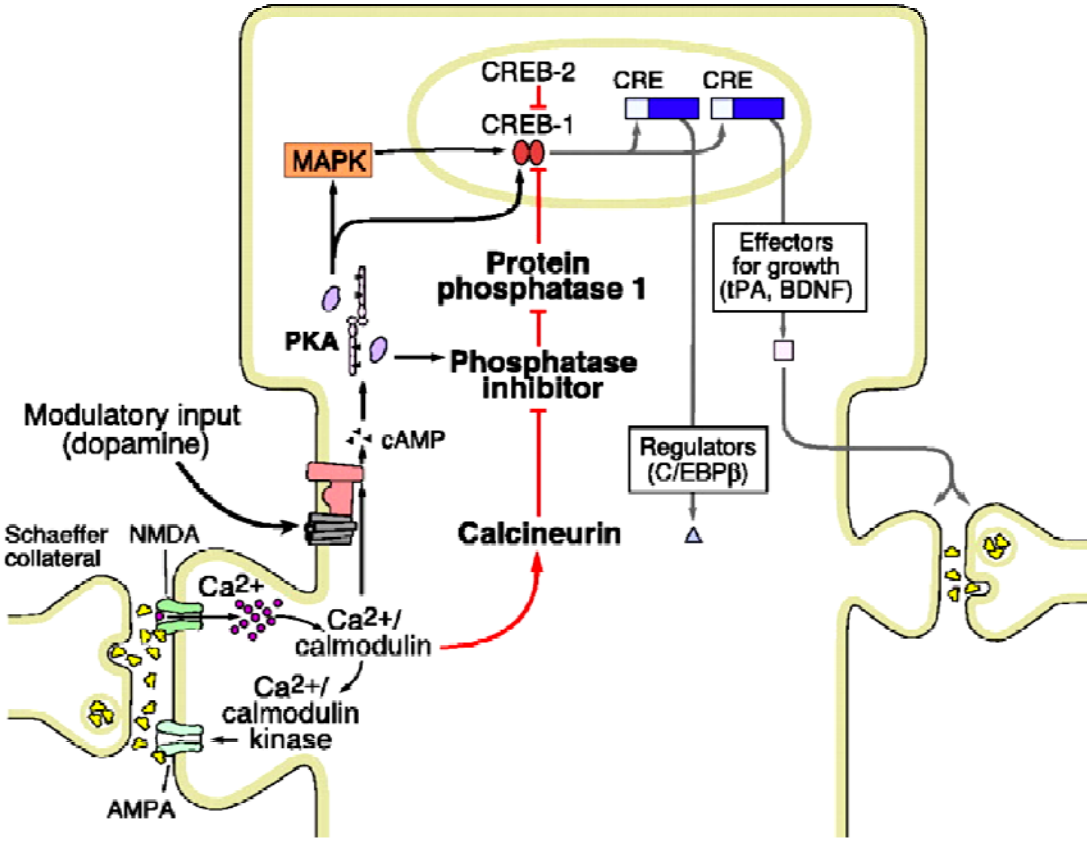


Importance of the phenotype

- heritable
- reliable and valid assessment
- biological correlate

Memory

Molecular cascade

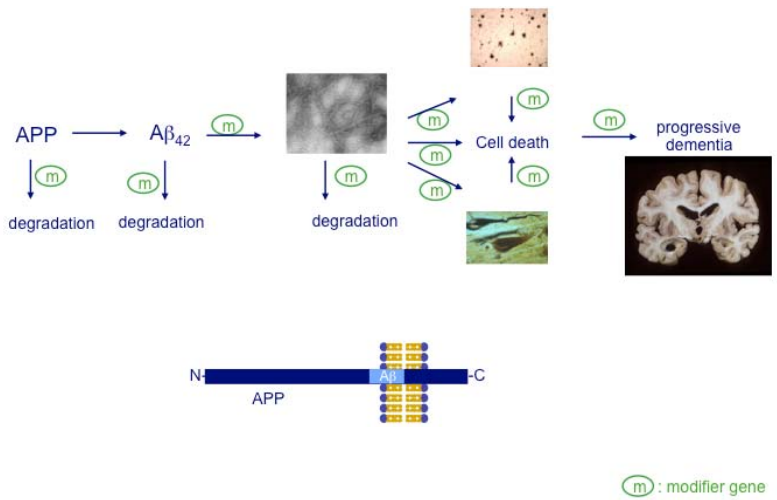


Kandel, *Science, 2001*

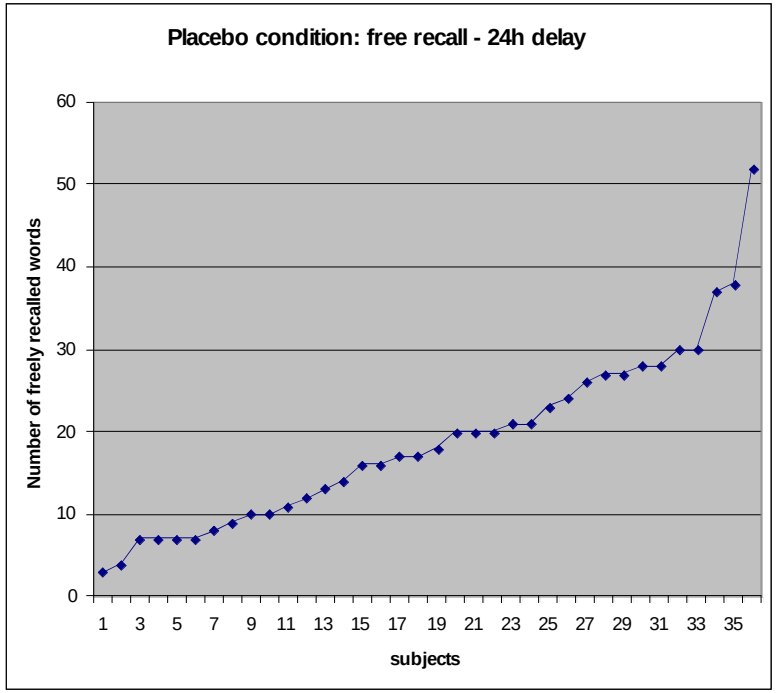
Molecular cascade in humans?

Importance of human genetic research

Identification of memory-related molecules

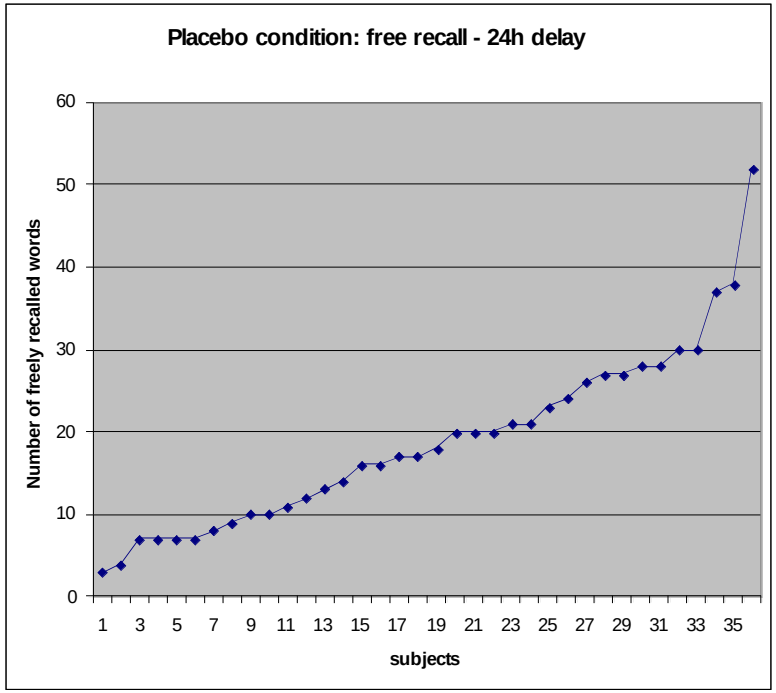


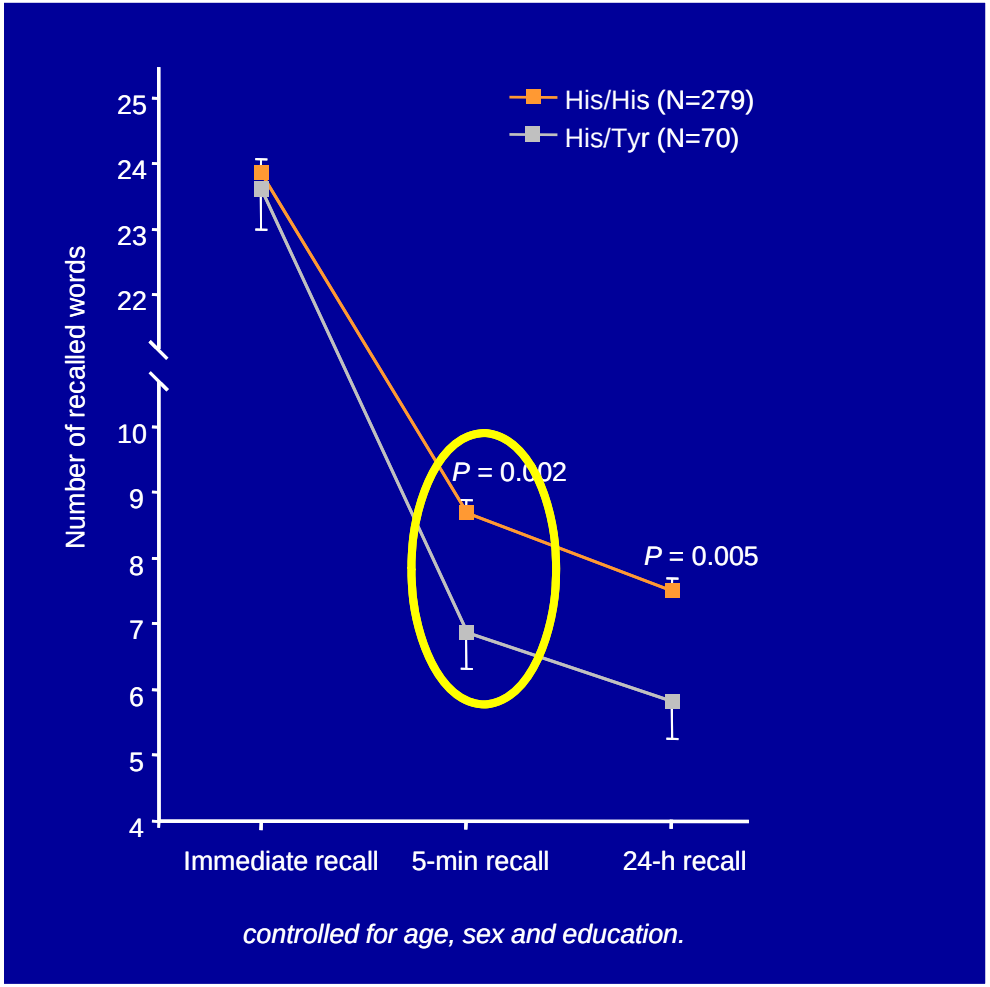
Important: Physiological variability



- Heritability: 50%
- Genes?

5-HT2a receptor gene





de Quervain, Henke, Aerni, Coluccia, Wollmer, Hock, Nitsch, Papassotiropoulos
***Nature Neuroscience* (2003)**

Importance of human genetic research

Understanding of neural mechanisms

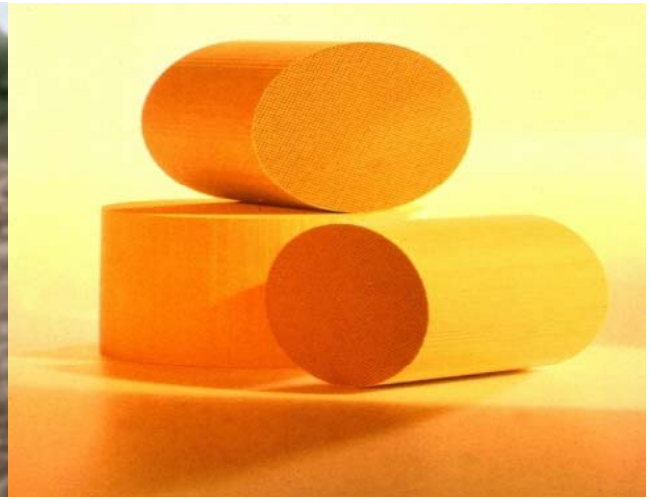
Emotional Memory

- Variability?
- Genes?

Emotional Memory

- 435 participants
- Emotional and neutral photographs

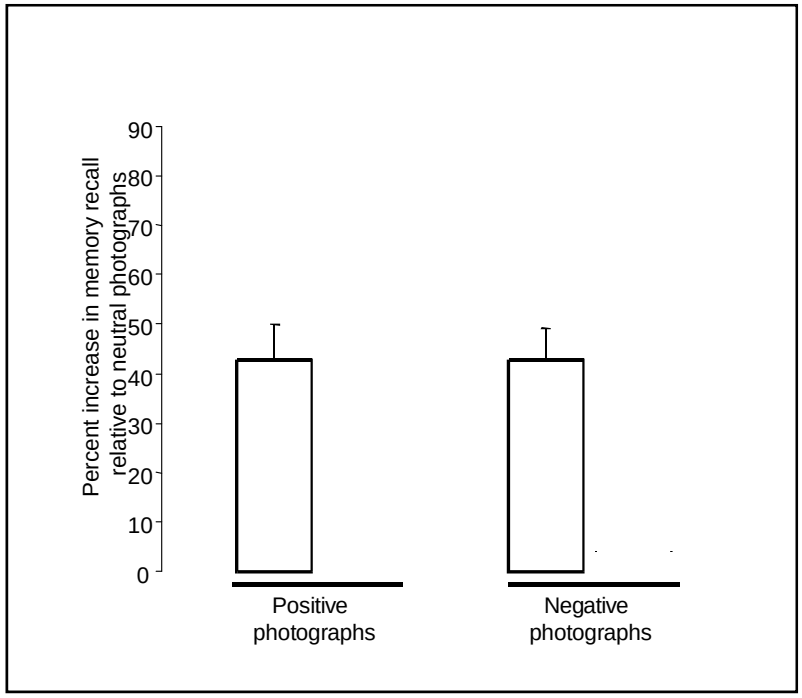




de Quervain, Kolassa, Ertl, Lamaro Onyut, Neuner, Elbert & Papassotiropoulos
Nature Neuroscience, 2007

α2B-adrenergic receptor

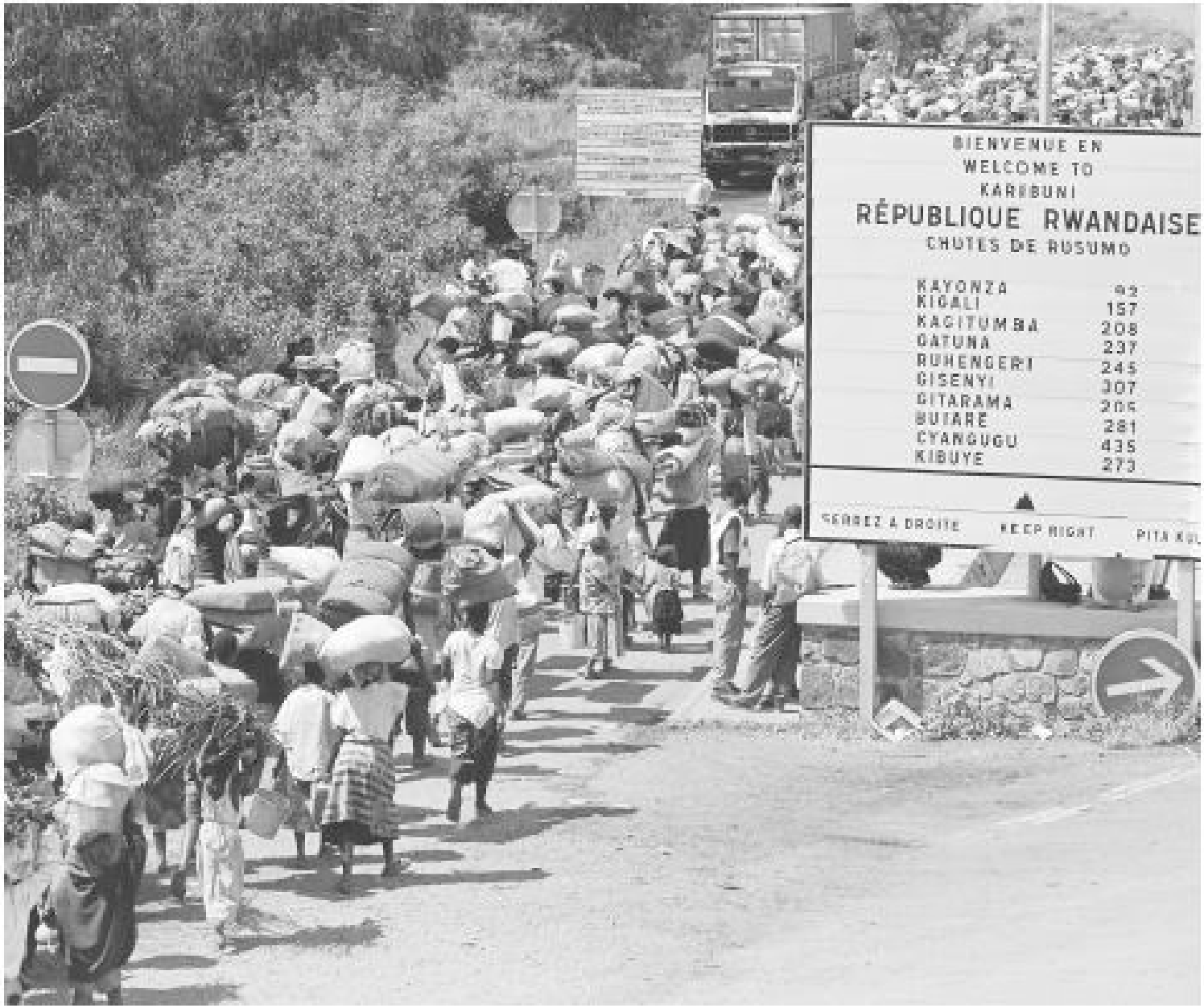
435 healthy young Swiss subjects



Traumatic memory?

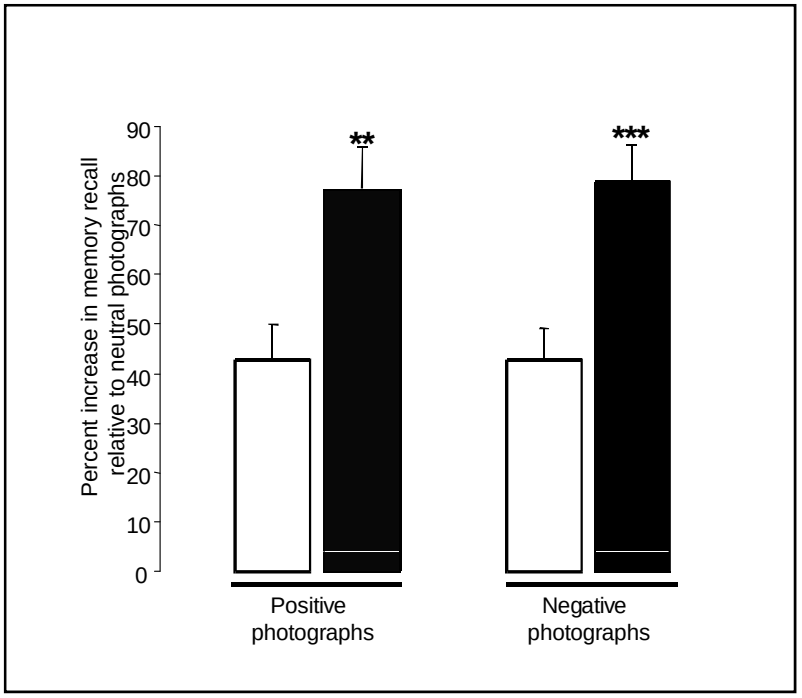
de Quervain, Kolassa, Ertl, Onyut, Neuner, Elbert, Papassotiropoulos, *Nature Neuroscience 2007*

Traumatic Memory

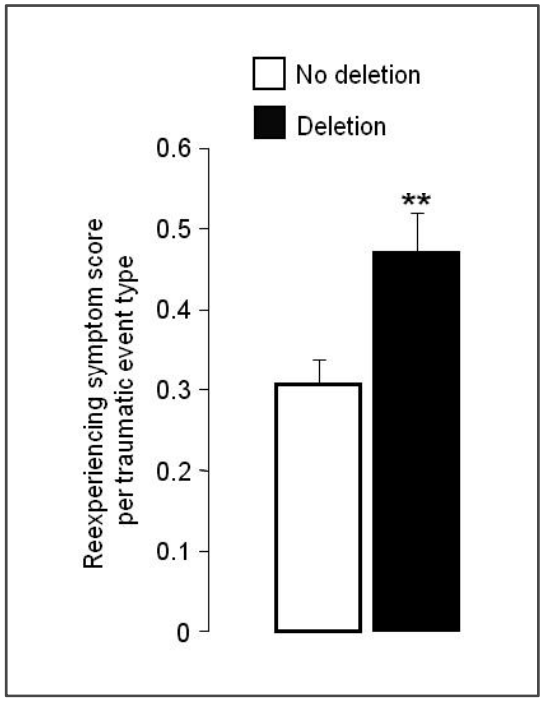


α2B-adrenergic receptor

435 healthy young Swiss subjects



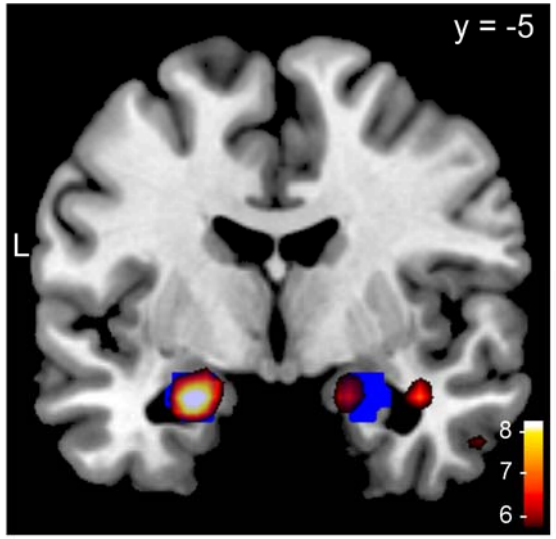
202 survivors of the Rwandan genozide



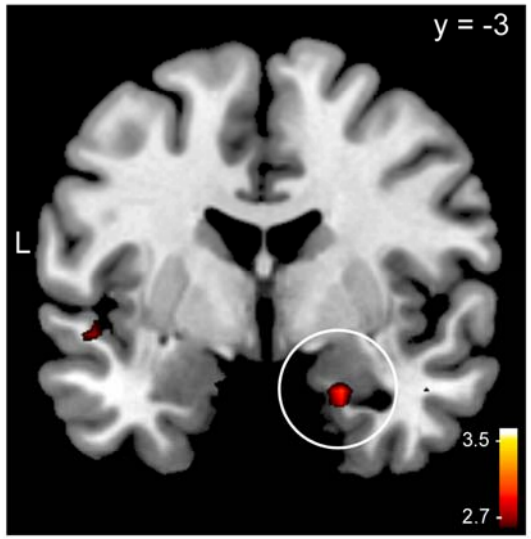
Physiology => Pathophysiology

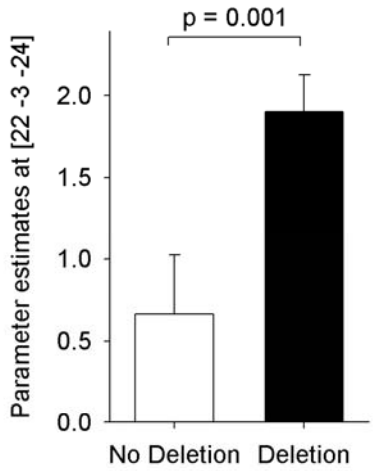
de Quervain, Kolassa, Ertl, Onyut, Neuner, Elbert, Papassotiropoulos, *Nature Neuroscience 2007*

Neural Mechanisms: functional brain imaging



Genotype-independent amygdala activation during encoding of negative vs. neutral pictures.





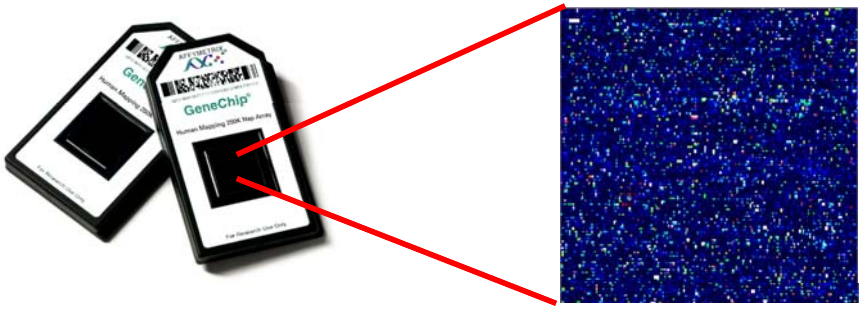
Genotype-dependent brain activity in the amygdala

Rasch et al., *PNAS*, 2009

Importance of human genetic research

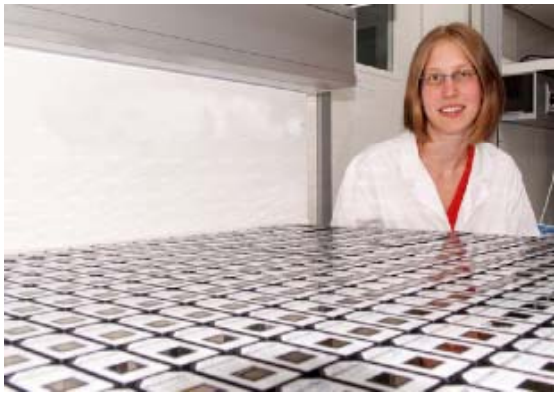
Identification of potential drug targets

High-throughput genome scans



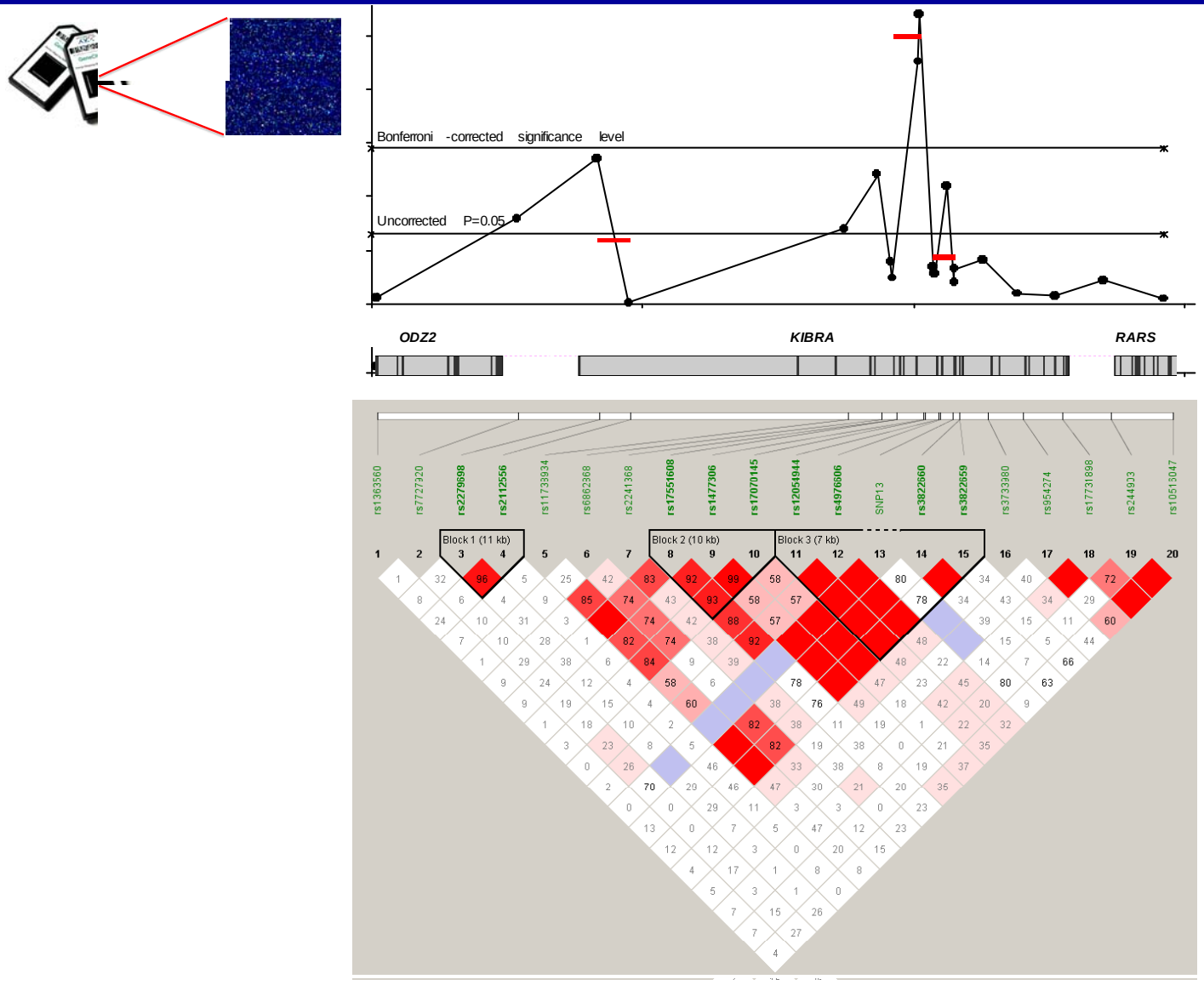
> 900000 SNPs
> 900000 probes for CNVs

Hybridization Washing Scanner



Standardized processing enables the study of large populations

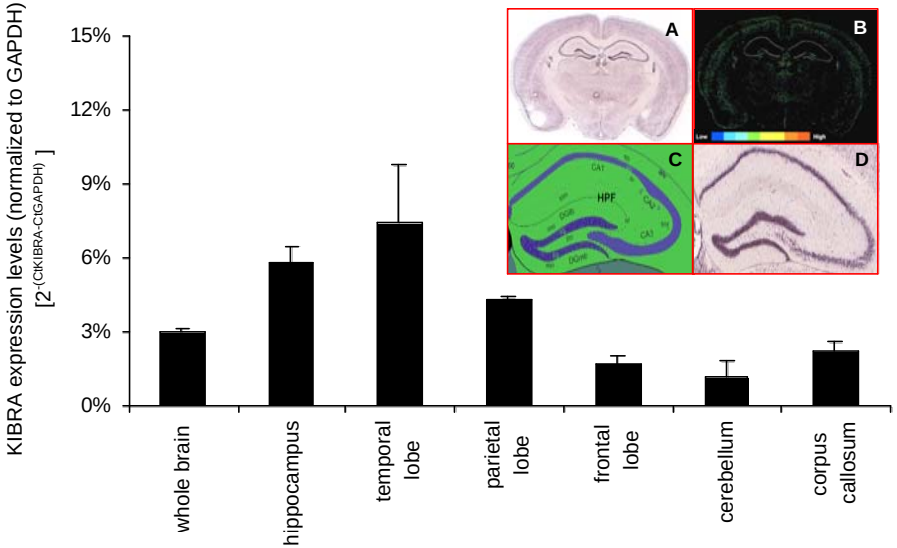
KIBRA



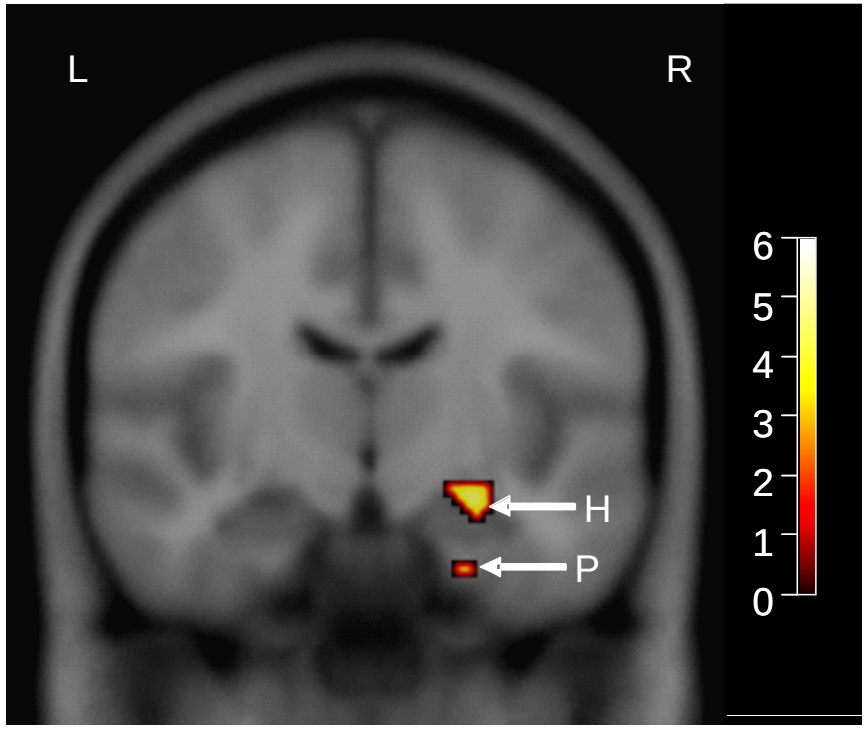
Papassotiropoulos et al. *Science, 2006*

KIBRA

Gene expression



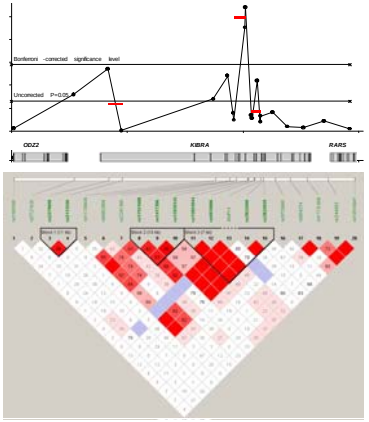
fMRI



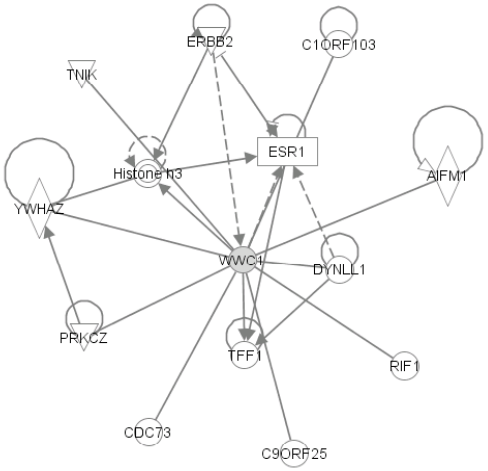
Papassotiropoulos et al. *Science, 2006*

Genetic Information => Drug targets

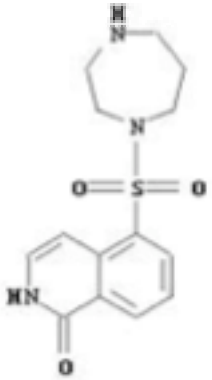
KIBRA



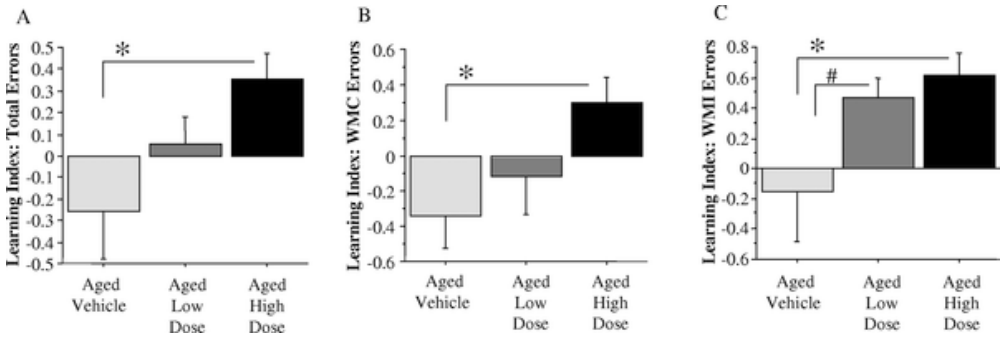
Pathway



Fasudil



Treatment



Huentelman et al., 2009

Importance of human genetic research

Avoid erroneous interpretations!

OR: the difference between group statistics and individual trait status is huge!
(…but notoriously difficult to explain)

Misconceptions

Alcoholism-Depression Gene ID'd!

Am I gene carrier?

Personalized medicine?

Health and Traits – List of Conditions – 23andMe

https://www.23andme.com/health/all/

23andMe genetics just got personal.

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health reports: complete list

The 23andMe service includes genetic analysis on all of the following diseases and conditions. This list grows every month as new research is published.

*** Established Research Reports**
Established Research reports give you information about conditions and traits for which there are genetic associations supported by multiple, large, peer-reviewed studies. Because these associations are widely regarded as reliable, we use them to develop quantitative estimates and explanations of what they mean for you.

Preliminary Research Reports
Preliminary Research reports are based on peer-reviewed, published research where the findings still need to be confirmed by the scientific community. They also include topics where there may be contradictory evidence. Topics may move from Preliminary Research to Established Research when and if sufficient follow-up studies are performed. New discoveries in genetics are being published all the time and we strive to keep our customers updated with the latest information on genetics and health.

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Carrier Status (24)
Alpha-1 Antitrypsin Deficiency *
BRCA Cancer Mutations (Selected) *
Bloom's Syndrome *
Canavan Disease *
Connexin 26-Related Sensorineural Hearing Loss *
Cystic Fibrosis *
Factor XI Deficiency *
Familial Dysautonomia *
Familial Hypercholesterolemia Type B *
Familial Mediterranean Fever *
Fanconi Anemia (FANCC-related) *
G6PD Deficiency *
Gaucher Disease *
Glycogen Storage Disease Type 1a *
Hemochromatosis *
Limb-girdle Muscular Dystrophy *
Maple Syrup Urine Disease Type 1B *

Disease Risk (112)
Abdominal Aortic Aneurysm
Age-related Macular Degeneration *
Alcohol Dependence
Alopecia Areata
Alzheimer's Disease *
Ankylosing Spondylitis
Asthma
Atopic Dermatitis
Atrial Fibrillation *
Atrial Fibrillation: Preliminary Research
Attention-Deficit Hyperactivity Disorder
Back Pain
Basal Cell Carcinoma
Behçet's Disease
Bipolar Disorder *
Bipolar Disorder: Preliminary Research
Bladder Cancer

Personalized medicine?

Colorectal Cancer
Exfoliation Glaucoma
Heart Attack
Lung Cancer
Lupus (Systemic Lupus Erythematosus)
Multiple Sclerosis
Obesity
Abdominal Aortic Aneurysm
Attention-Deficit Hyperactivity Disorder
Alcohol Dependence
Ankylosing Spondylitis
Antidepressant Response
Asthma
Atrial Fibrillation
Avoidance of Errors
Back Pain
Baldness
Basal Cell Carcinoma
Beta-Blocker Response
Bipolar Disorder: Preliminary Research
Birth Weight
Bladder Cancer
Blood Glucose
Brain Aneurysm
Breast Cancer Risk Modifiers
Breastfeeding and IQ
C-reactive Protein Level
Caffeine Metabolism
Celiac Disease: Preliminary Research
Chronic Lymphocytic Leukemia
Cleft Lip and Cleft Palate
Cluster Headaches
Creutzfeldt-Jakob Disease
Developmental Dyslexia
Endometriosis
Esophageal Cancer
Essential Tremor
Eye Color
Food Preference
Freckling
Gallstones

Hair Color
Hair Thickness
HDL Cholesterol Level
Height
Heroin Addiction
HIV Progression
High Blood Pressure (Hypertension)
Intrahepatic Cholestasis of Pregnancy
Kidney Disease
Larynx Cancer
Longevity
Lou Gehrig's Disease (ALS)
Male Infertility
Measures of Intelligence
Memory
Neuroblastoma
Nicotine Dependence
Obesity: Preliminary Research
Obsessive-Compulsive Disorder
Odor Detection
Oral and Throat Cancer
Osteoarthritis
Pain Sensitivity
Parkinson's Disease: Preliminary Research
Peripheral Arterial Disease
Persistent Fetal Hemoglobin
Placental Abruption
Preeclampsia
Progressive Supranuclear Palsy
Schizophrenia
Sjögren's Syndrome
Cutaneous Melanoma
Statin Response
Stomach Cancer
Tardive Dyskinesia
Thyroid cancer
Tourette's Syndrome
Tuberculosis
Uterine Fibroids
Restless Legs Syndrome
Ulcerative Colitis

Personalized medicine?

About Memory

Studies of twins suggest that genetics has about the same influence as training and other environmental factors on a person's ability to remember a limited number of items over periods of seconds to minutes. That type of recall, referred to by psychologists as short-term memory, is maintained by temporary patterns of brain activity. But long-term memory creates lasting connections between brain cells that can potentially last a lifetime.

Research Report

This Research Report includes results from studies that still need to be confirmed by the scientific community. It also includes topics where there may be contradictory evidence. The results of these studies are not conclusive.

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Episodic memory

Journal	*Science*
Study Size	👪
Replications	None
Contrary Studies	None
Applicable Ethnicities	European
Marker	rs17070145

In this study, the authors asked people to read or listen to lists of words and then recall them later. People with at least one T at rs17070145 performed about 20% better than those with a C at both copies of the SNP five minutes and 24 hours after seeing or hearing the lists. The SNP lies within a gene called KIBRA that is thought to be involved with episodic memory, which involves the recall of events rather than information. (Note: the KIBRA gene is listed in the Genome Explorer as WWC1.)

Who	Genotype	What It Means
	TT	Slightly increased episodic memory.
Greg Mendel (Dad)	CT	Slightly increased episodic memory.
	CC	Typical episodic memory.

!

Citations

Papassotiropoulos A et al. (2006) . "Common Kibra alleles are associated with human memory performance." *Science* 475-8.

Personalized medicine?

- *Any one have the gene for increased memory?*
- *I have it and was wondering how common it is?*
- *I thought I did…CC*

	n	No. of words recalled		
		Immediately	After 5 min	After 24 hours
rs17070145				
CC	164	23.6 ± 0.3	7.6±0.2*	6.7 ± 0.2†
CT/TT	169	24.1 ± 0.3	9.4±0.2*	8.0 ± 0.2†
rs6439886				
TT	265	23.9 ± 0.2	8.4±0.2‡	7.3 ± 0.2§
TC/CC	76	24.2 ± 0.4	9.8±0.4‡	8.4 ± 0.4§

*$P = 0.000004$ †$P = 0.0008$ ‡$P = 0.002$ §$P = 0.022$

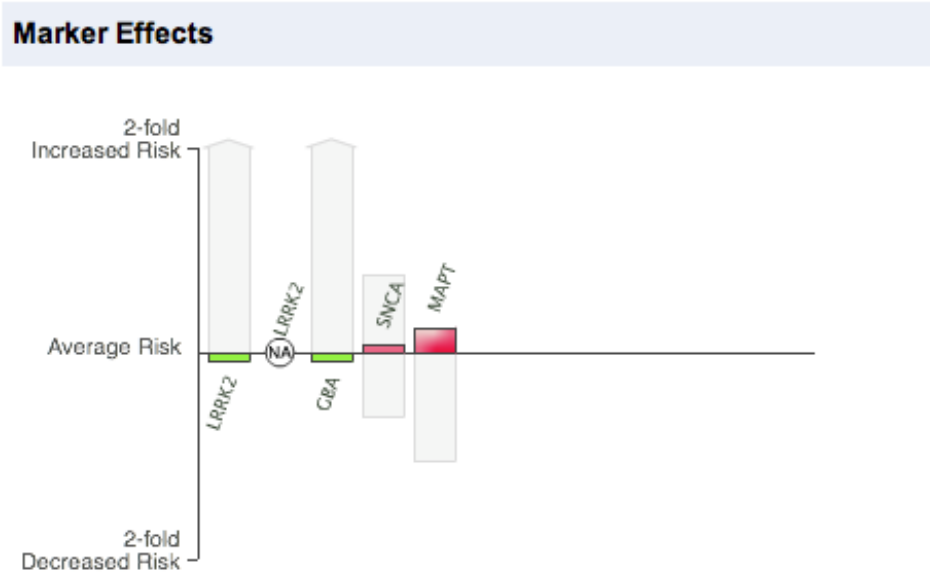
Papassotiropoulos et al. *Science, 2006*

Importance of human genetic research

Avoid erroneous interpretations!

OR: Never simply add population-derived risks to “predict” an individual’s risk!
(…also notoriously difficult to explain)

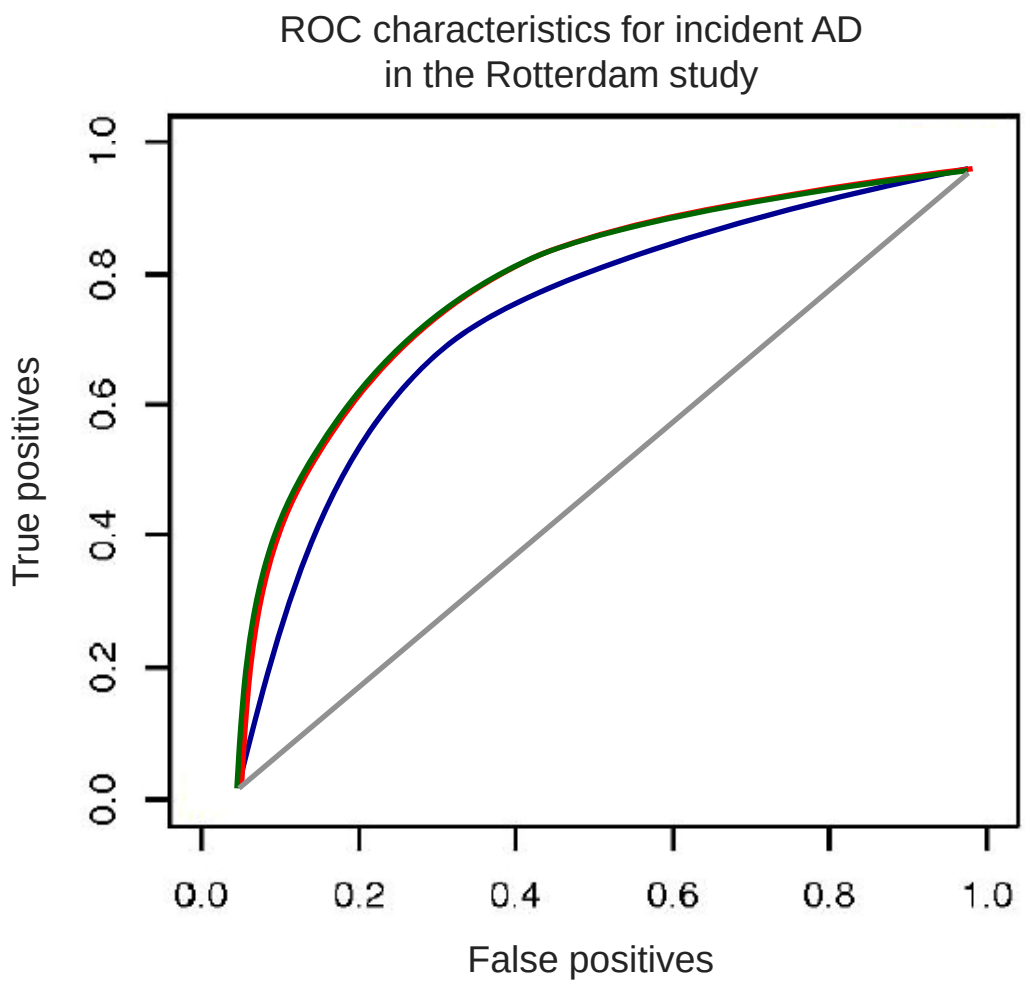
Individual risk assessment



- A simple addition implies that the effects are independent of each other
- A simple addition ignores the importance of gene-gene and gene-environment interactions

Improving prediction?

Improving prediction?



Model incorporating:
Age and Sex alone

Model incorporating:
Age, Sex, *APOE*

Model incorporating:
Age, Sex, *APOE, CLU, PICALM*

Seshadri et al. *JAMA, 2010*

Improving prediction?

A multilocus genetic risk score for coronary heart disease: case-control and prospective cohort analyses

Samuli Ripatti, Emmi Tikkanen, Marju Orho-Melander, Aki S Havulinna, Kaisa Silander, Amitabh Sharma, Candace Guiducci, Markus Perola, Antti Jula, Juha Sinisalo, Marja-Liisa Lokki, Markku S Nieminen, Olle Melander, Veikko Salomaa, Leena Peltonen, Sekar Kathiresan*

Summary

Background Comparison of patients with coronary heart disease and controls in genome-wide association studies has revealed several single nucleotide polymorphisms (SNPs) associated with coronary heart disease. We aimed to establish the external validity of these findings and to obtain more precise risk estimates using a prospective cohort design.

Methods We tested 13 recently discovered SNPs for association with coronary heart disease in a case-control design including participants differing from those in the discovery samples (3829 participants with prevalent coronary heart disease and 48 897 controls free of the disease) and a prospective cohort design including 30 725 participants free of cardiovascular disease from Finland and Sweden. We modelled the 13 SNPs as a multilocus genetic risk score and used Cox proportional hazards models to estimate the association of genetic risk score with incident coronary heart disease. For case-control analyses we analysed associations between individual SNPs and quintiles of genetic risk score using logistic regression.

Findings In prospective cohort analyses, 1264 participants had a first coronary heart disease event during a median 10·7 years' follow-up (IQR 6·7–13·6). Genetic risk score was associated with a first coronary heart disease event. When compared with the bottom quintile of genetic risk score, participants in the top quintile were at 1·66-times increased risk of coronary heart disease in a model adjusting for traditional risk factors (95% CI 1·35–2·04, p value for linear trend=$7 \cdot 3 \times 10^{-10}$). Adjustment for family history did not change these estimates. Genetic risk score did not improve C index over traditional risk factors and family history (p=0·19), nor did it have a significant effect on net reclassification improvement (2·2%, p=0·18); however, it did have a small effect on integrated discrimination index (0·004, p=0·0006). Results of the case-control analyses were similar to those of the prospective cohort analyses.

The Lancet, 2010

Personalized medicine?

Psynomics – Genomics For The New Psychiatry

http://www.psynomics.com/

psynomics

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Welcome to Psynomics

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Our first two products:

Psynome™ – tests for two mutations of a gene that are associated with bipolar disorder.

Psynome2™ –tests for gene mutations in the Promoter L allele gene that predicts patient response to serotonin-based drugs, the most commonly prescribed drug therapies in psychiatry today. These tests are useful to your doctor in making a timely and accurate diagnosis of your condition and prescribing the right medication. The tests can be ordered individually or combined.

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Personalized medicine?

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GENETIC ANSWERS FOR THE NEW ERA IN NEUROPSYCHIATRY

home

The Mark-C test: message from the company

NeuroMark congratulates scientists from the Genetic Basis of Mood and Anxiety Disorders Unit and the Laboratory of Molecular Pathophysiology, Mood and Anxiety Program, National Institute of Mental Health, Bethesda, MD; Departments of Clinical Sciences and Psychiatry, University of Texas Southwestern Medical Center, Dallas; Genometrics Section, Inherited Disease Research Branch, National Human Genome Research Institute, NIH, Baltimore; and Mount Sinai School of Medicine, New York, on their precedent-setting discoveries of genetic markers of suicidal ideation emerging

Personalized medicine?

Article

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

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Objective: Suicidal ideation is an uncommon symptom than can emerge during antidepressant treatment. The biological basis of treatment-emergent suicidal ideation is unknown. Genetic markers may shed light on the causes of treatment-emergent suicidal ideation and help identify individuals at high risk who may benefit from closer monitoring, alternative treatments, or specialty care.

Method: A clinically representative cohort of outpatients with major depressive disorder who enrolled in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial were treated with citalopram under a standard protocol for up to 14 weeks. DNA samples from 1,915 participants were genotyped for 768 single-nucleotide polymorphisms in 68 candidate genes. Allele and genotype frequencies were compared between the 120 participants who developed treatment-emergent suicidal ideation and those who did not.

Results: Two markers were significantly associated with treatment-emergent suicidal ideation in this sample (marker rs4825476, p=0.0000784, odds ratio=1.94; permutation p=0.01; marker rs2518224, p=0.0000243, odds ratio=8.23; permutation p=0.003). These markers reside within the genes GRIA3 and GRIK2, respectively, both of which encode ionotropic glutamate receptors.

Conclusions: Markers within GRIK2 and GRIA3 were associated with treatment-emergent suicidal ideation during citalopram therapy. If replicated, these findings may shed light on the biological basis of this potentially dangerous adverse event and help identify patients at increased risk.

(Am J Psychiatry 2007; 164:1530–1538)

Personalized medicine

Companies address important issues, BUT

Many implications not supported by current data!!

Personalized medicine

naturenews

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Published online 23 November 2009 | Nature | doi:10.1038/news.2009.1102

News

Diagnosing the future of genomics

Eric Green discusses his priorities as newly appointed director of the US National Human Genome Research Institute.

Erika Check Hayden

On 17 November, US National Institutes of Health (NIH) director Francis Collins named Eric Green as head of the National Human Genome Research Institute in Bethesda, Maryland — the post held by Collins before he became NIH director. Green talked to *Nature* about his plans for the institute, which has a budget of almost US$500

Eric Green is the new director of the US National Human Genome Research Institute.
M. Bartlett, NHGRI

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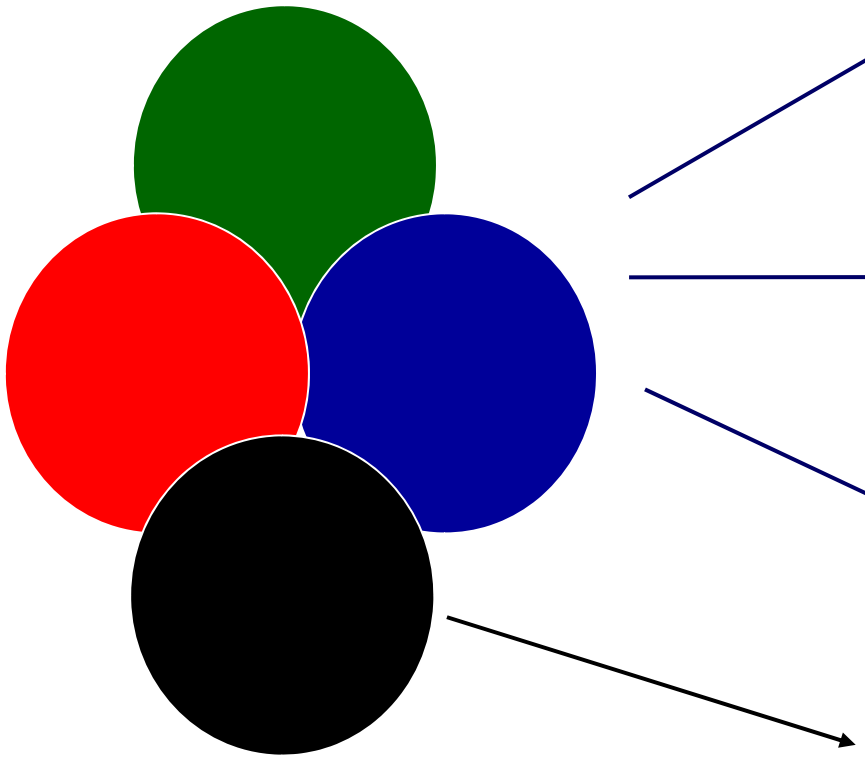
Personalized medicine

What advice would you have for people who are considering buying personal genomics services from a company to find out their genetic risk for common diseases?

I haven't yet gone to get that information, because I think that the amount of information available at this time wouldn't really change anything that I am doing. A lot of what I know about my own health is based on family history — I think that understanding family history, and making sure your physician knows that, is incredibly valuable, and that's where I would put my priority at the moment. But it is a changing landscape, so I don't think any advice I would give today would be the same a year from now.

Personalized medicine?



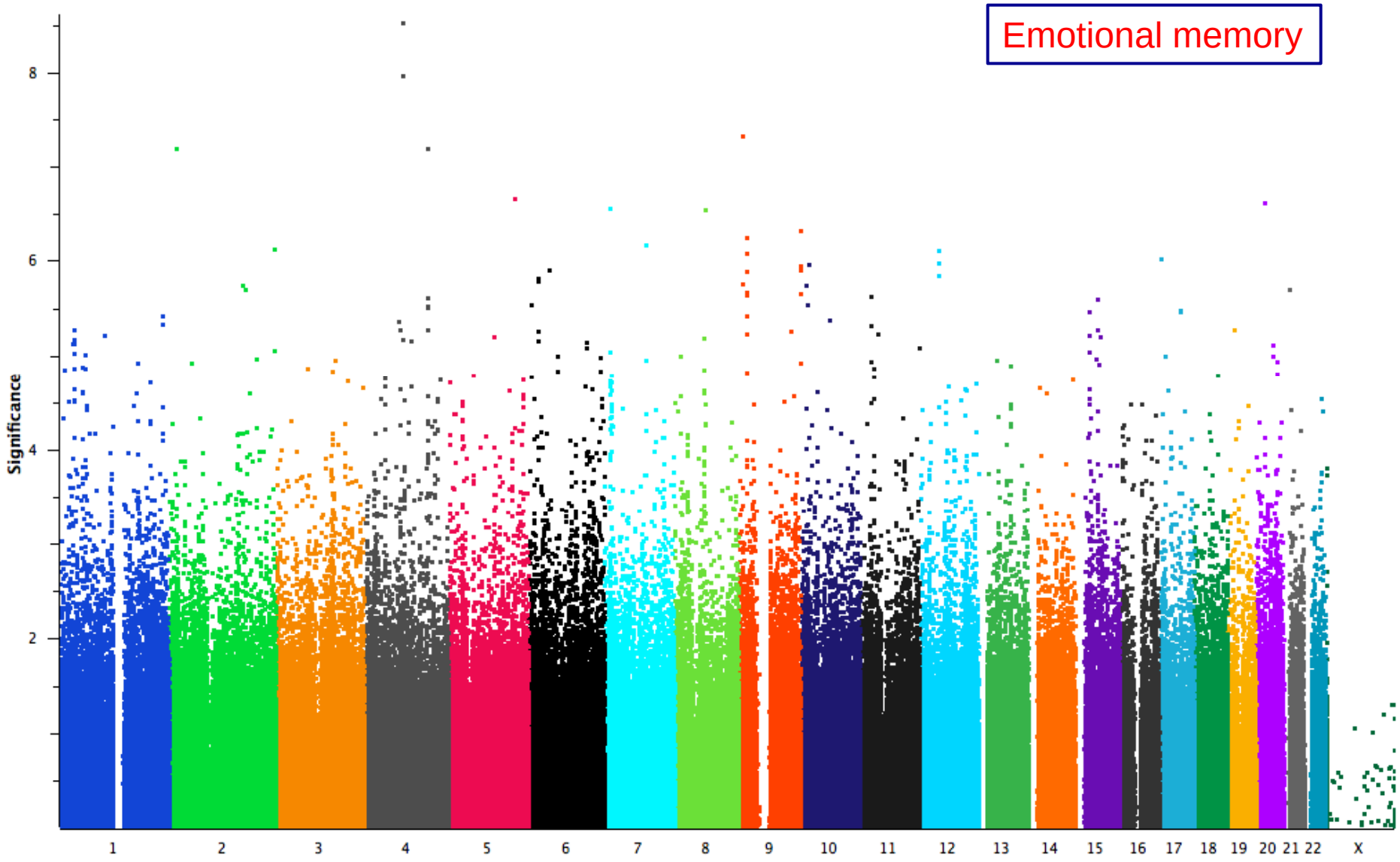
Prediction?

Diagnosis?

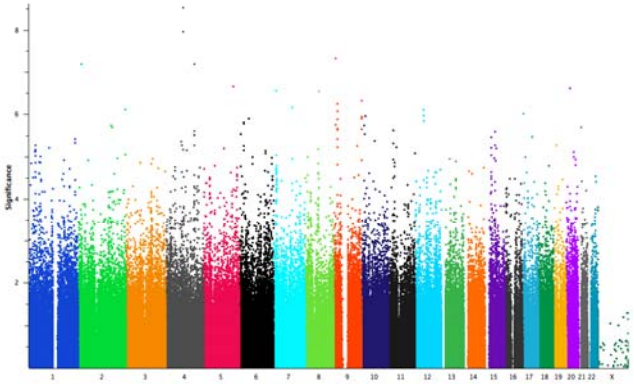
Pharmacogenomics?

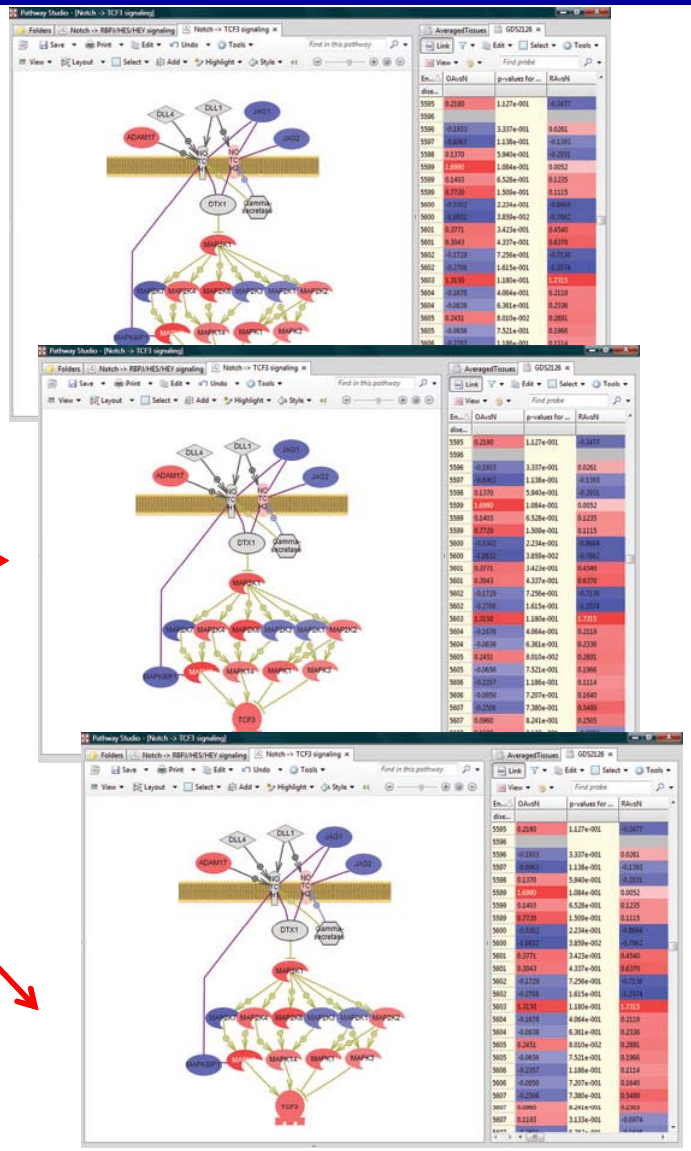
Understanding biology!
Identifying new therapeutic possibilities!

Our strategy

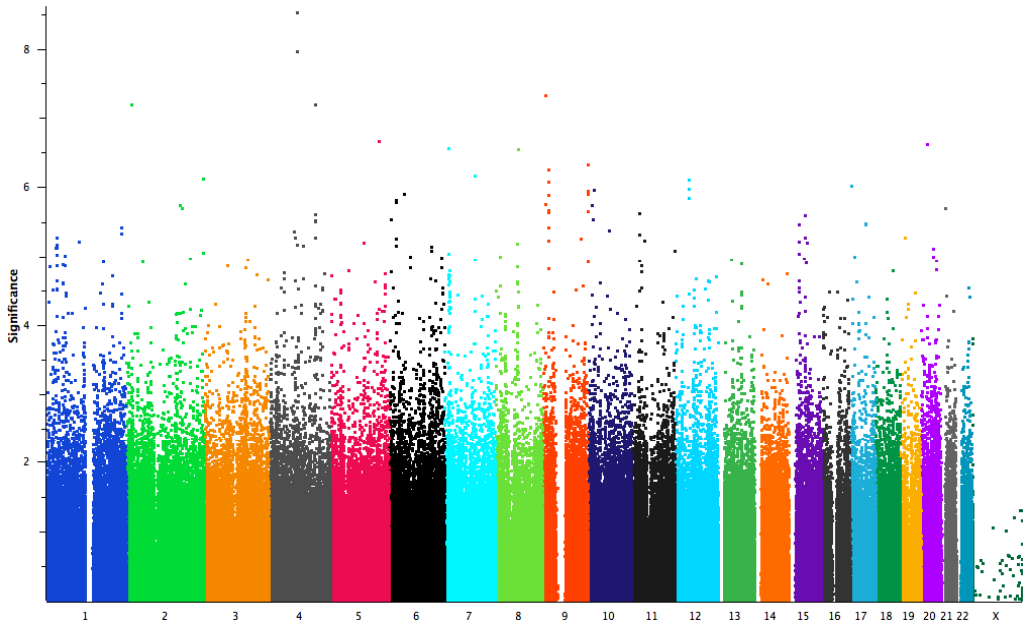


Use of entire genome, fit into pathways





A genome-guided clinical study of human memory

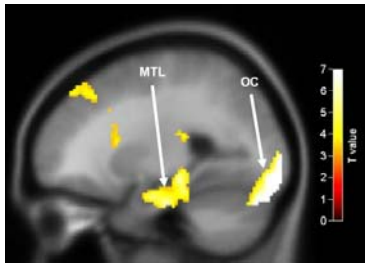


Phase II clinical trial, proof of concept


Trends in Cognitive Sciences
Special Issue:
The Genetics of Cognition
Cell PRESS
Trends Cogn. Sci. September 2011 Vol. 15 No. 9, pp. 375–446 ISSN 1364-6613

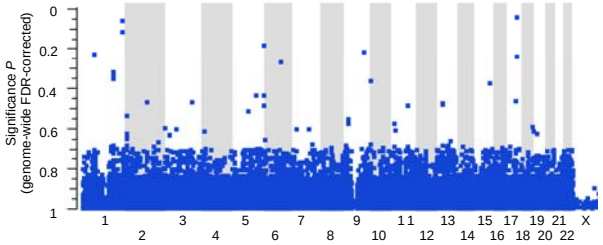
Our strategy

memory tasks in health and disease
N > 3500



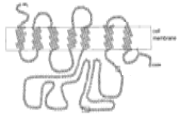
structural and functional brain imaging
N > 700

Genome-wide screens

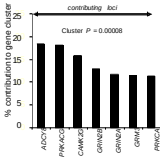


Clinical studies

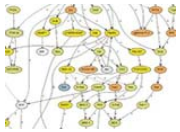
single loci



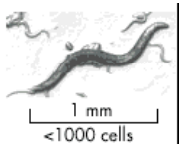
gene/loci groups



computational modeling



biological validation



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