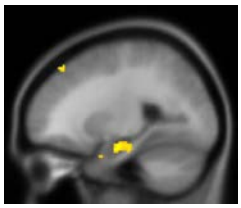
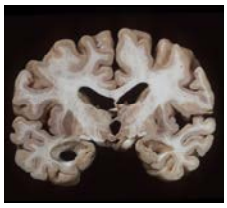
# Individualisierte Medizin: Hoffnung für die Zukunft oder eher eine Illusion?



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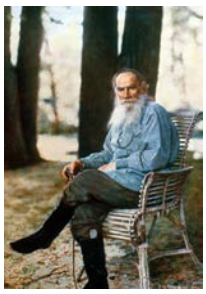
Life Sciences Training Facility, Biozentrum
University of Basel, Switzerland


*Rheinfelder Tage, Rheinfelden, 16. März 2012*

# Zitat zur individualisierten Medizin

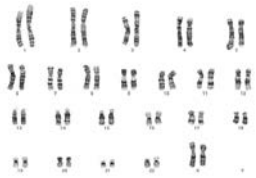
"Die Ärzte kamen sowohl einzeln als auch in Konsilien, redeten viel auf Französisch, auf Deutsch, auf Latein, missbilligten der eine den anderen, verschrieben die unterschiedlichsten Arzneien gegen alle ihnen bekannten Krankheiten; aber nicht einem von ihnen kam der einfache Gedanke in den Sinn, dass ihnen die Krankheit an der sie litt, nicht bekannt sein konnte,

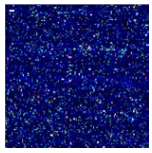
*Wie keine einzige Krankheit bekannt sein kann, von der ein lebendiger Mensch ergriffen ist: denn jeder lebendige Mensch hat seine Besonderheiten und immer eine besondere, ihm eigene neue, komplizierte, der Medizin unbekannte Krankheit …."*

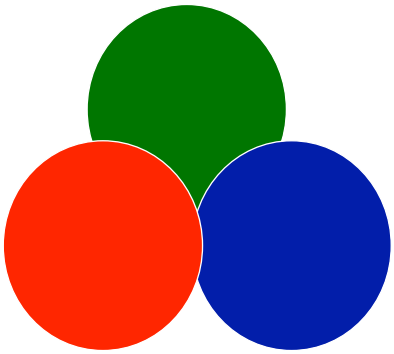


Krieg und Frieden
1869
Leo Tolstoy

## Individualisierte Medizin/Genetik?





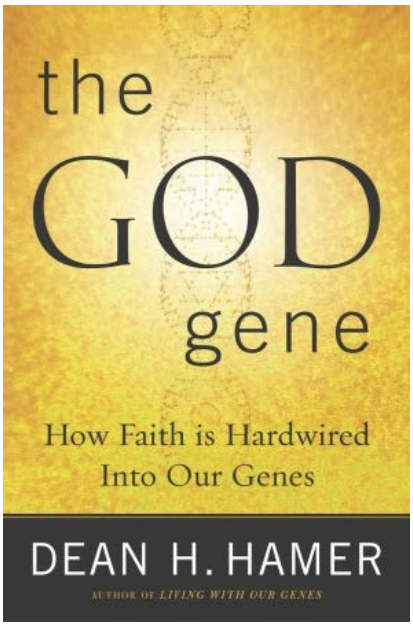


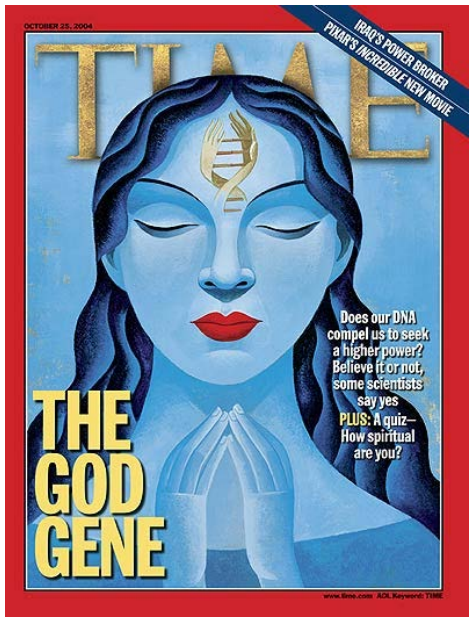
Prediction?

Diagnosis?

Pharmacogenomics?

## Wichtigkeit des Phänotyps



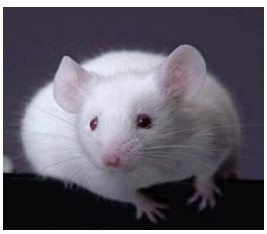



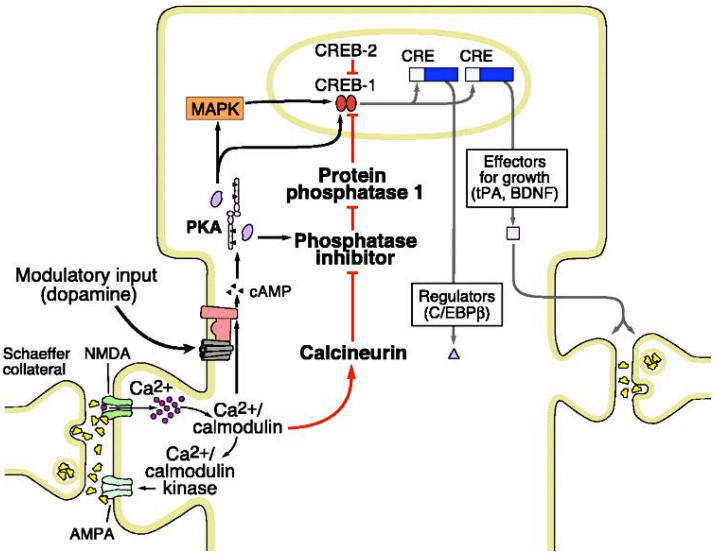
## Wichtigkeit des Phänotyps

- Heritabel
- Reliabel, Valide
- Biologisches Korrelat

Memory

## Molekulare Kaskade



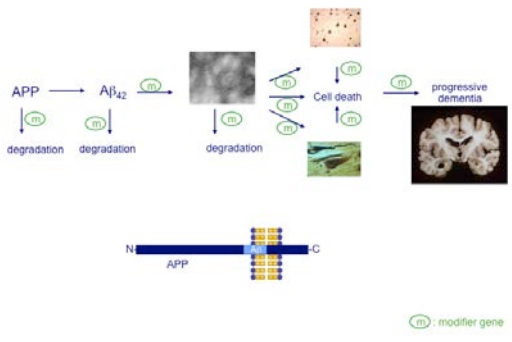



Kandel, *Science, 2001*

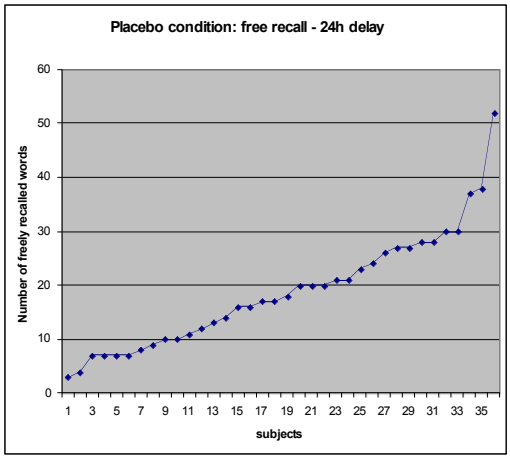
## Molekulare Kaskade beim Menschen?

## Wichtigkeit der humangenetischen Forschung

**Identifizierung von gedächtnis-relevanten Molekülen**

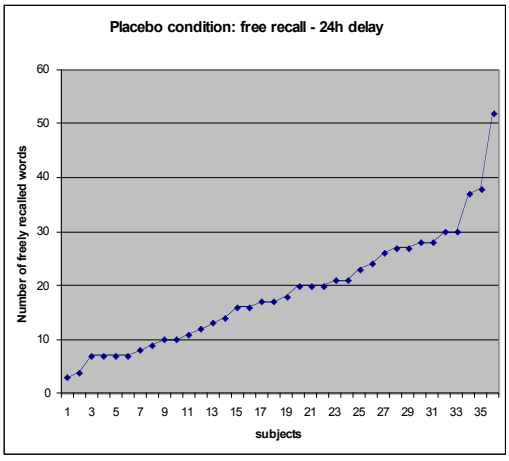


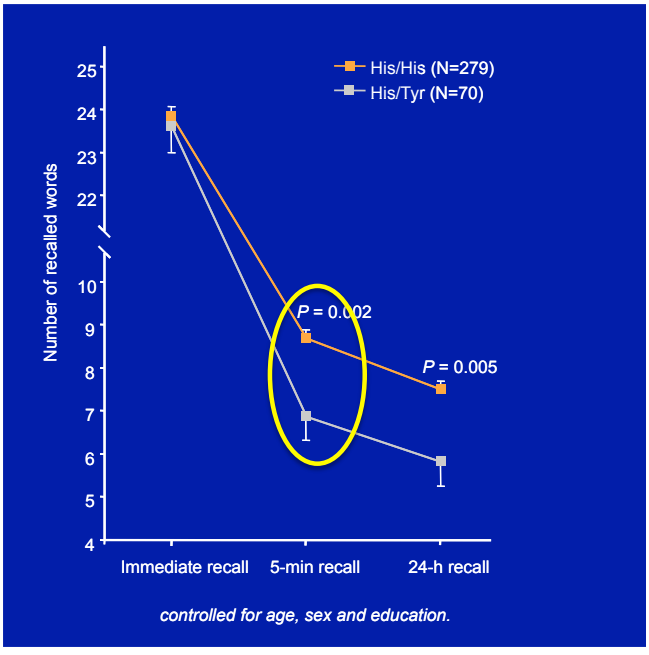
# Wichtig: Physiologische Variabilität




- Heritabilität: 50%
- Gene?

# 5-HT2a receptor gene




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

## Wichtigkeit der humangenetischen Forschung

Verständnis neuronaler Mechanismen

## Emotionales Gedächtnis


- Variabilität?
- Gene?

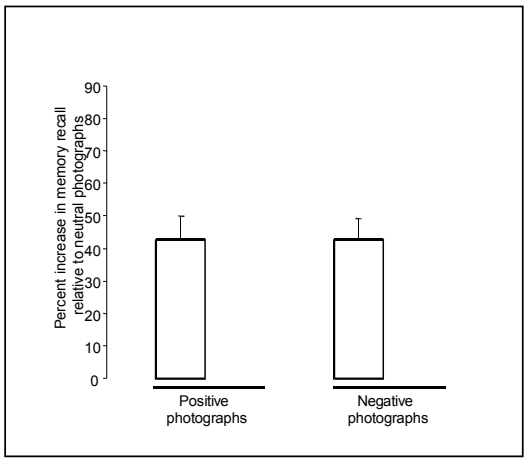
# Emotionales Gedächtnis

- 435 participants
- Emotional and neutral photographs

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

# α2B-adrenergic receptor

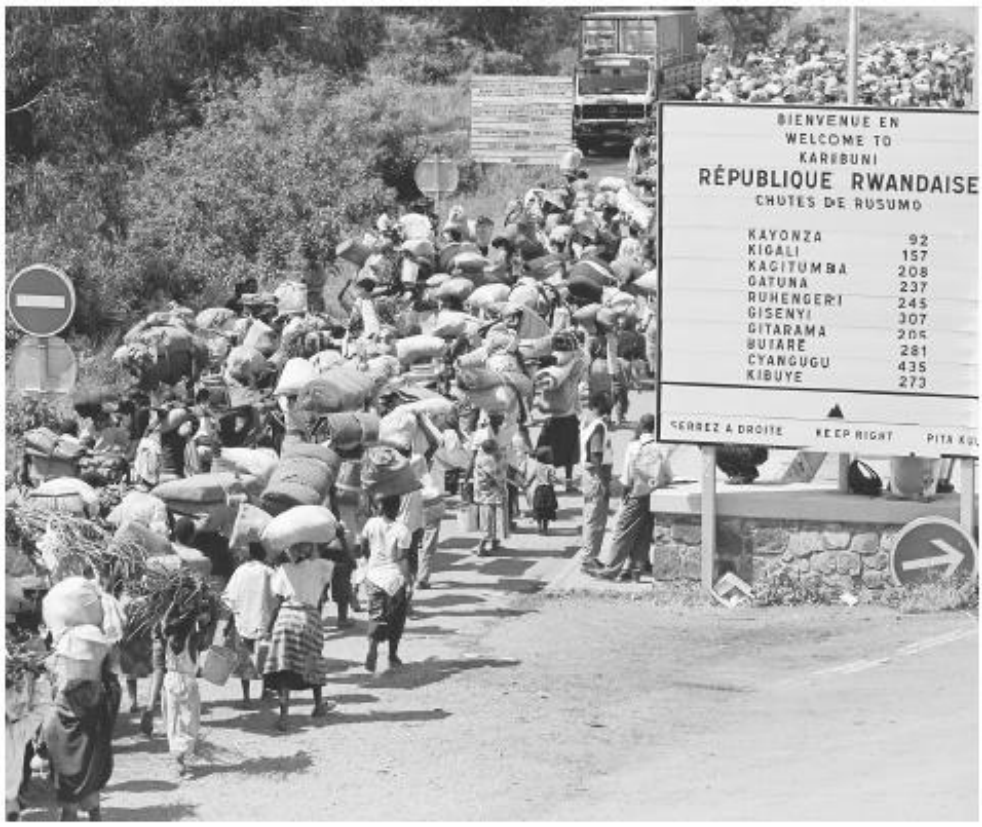
435 healthy young Swiss subjects




Traumatisches Gedächtnis?

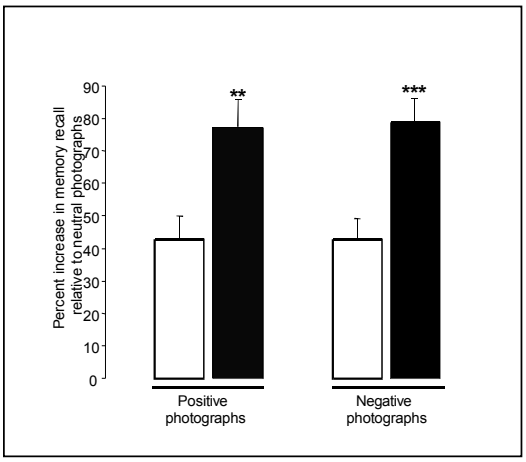
de Quervain, Kolassa, Ertl, Onyut, Neuner, Elbert, Papassotiropoulos, *Nature Neuroscience 2007*

# Traumatisches Gedächtnis

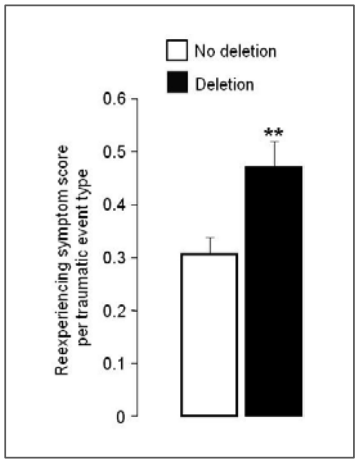



# α2B-adrenergic receptor

435 healthy young Swiss subjects



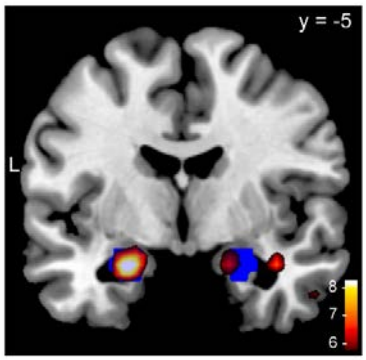

202 survivors of the Rwandan genozide



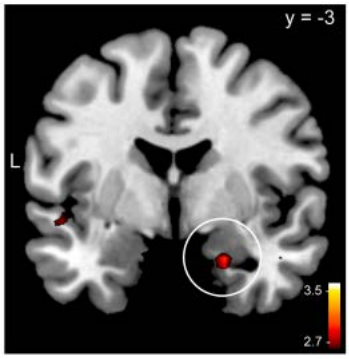

Physiologie => Pathophysiologie

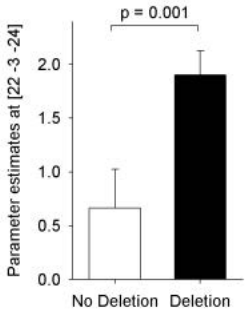
de Quervain, Kolassa, Ertl, Onyut, Neuner, Elbert, Papassotiropoulos, *Nature Neuroscience 2007*

# Funktionelle Bildgebung




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



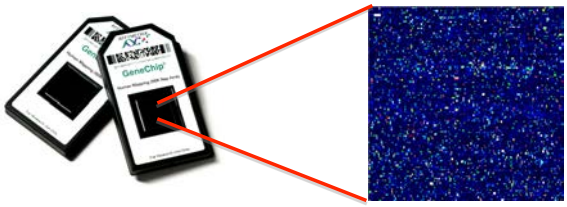

Genotype-dependent brain activity in the amygdala

Rasch et al., *PNAS*, 2009

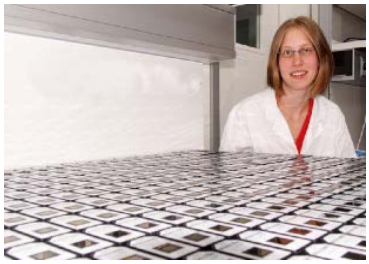
# Wichtigkeit der humangenetischen Forschung

Identifizierung von potentiellen Medikamenten

# High-throughput genome scans

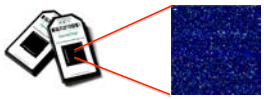


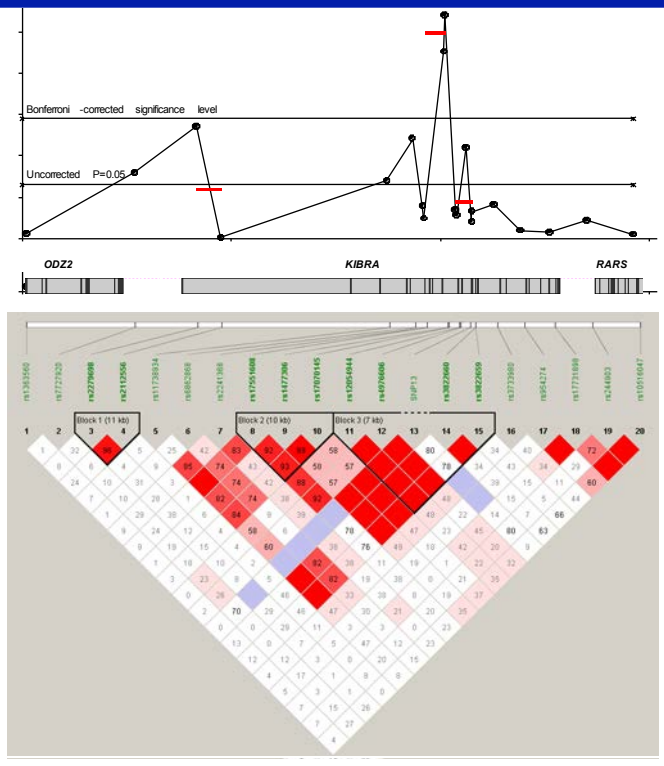
> 900000 SNPs
> 900000 probes for CNVs

Standardized processing enables the study of large populations

# KIBRA

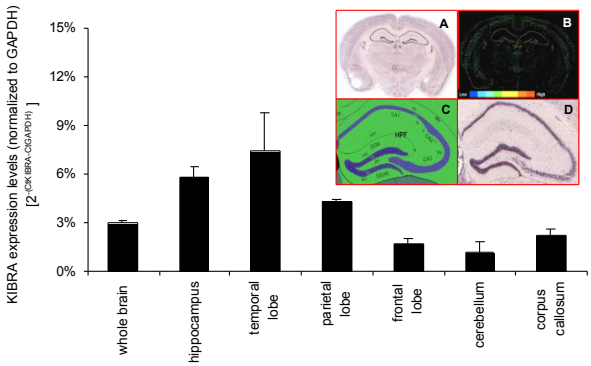




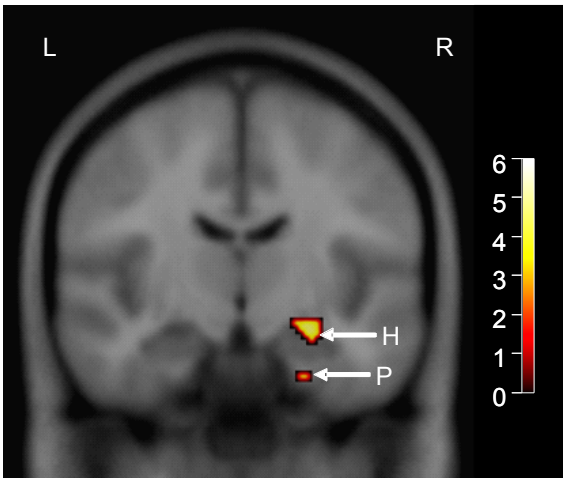

Papassotiropoulos et al. *Science, 2006*

# KIBRA

## Gene expression



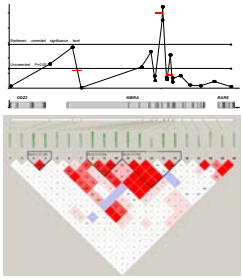

## fMRI



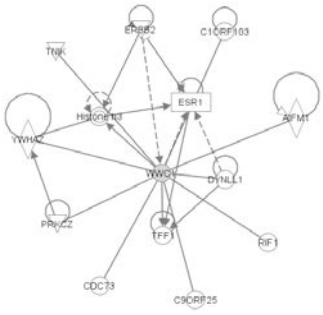

Papassotiropoulos et al. *Science, 2006*

# Genetic Information => Drug targets

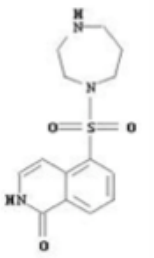
## KIBRA



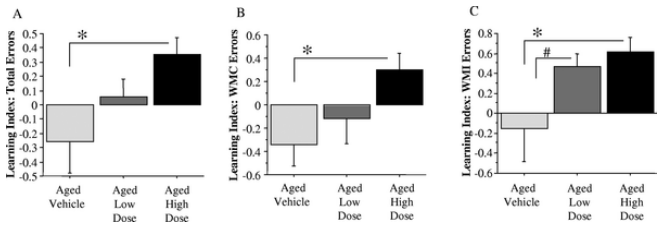
## Pathway




## Fasudil



## Treatment




Huentelman et al., 2009

## Wichtigkeit der humangenetischen Forschung

# Falsche Schlüsse vermeiden!

ODER: Der Unterschied zwischen Gruppenstatistik und Individuum ist gross!
*(…aber sehr schwer zu vermitteln)*

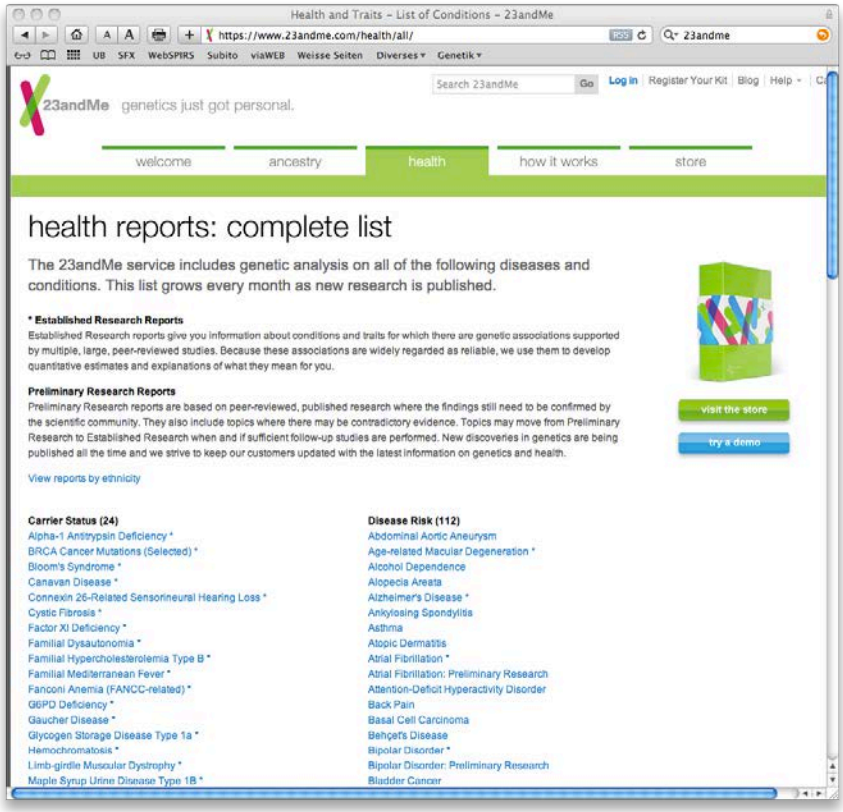
## Fehler

CBS NEWS

**Alcoholism-Depression Gene ID'd!**

*Habe ich das Gen?*

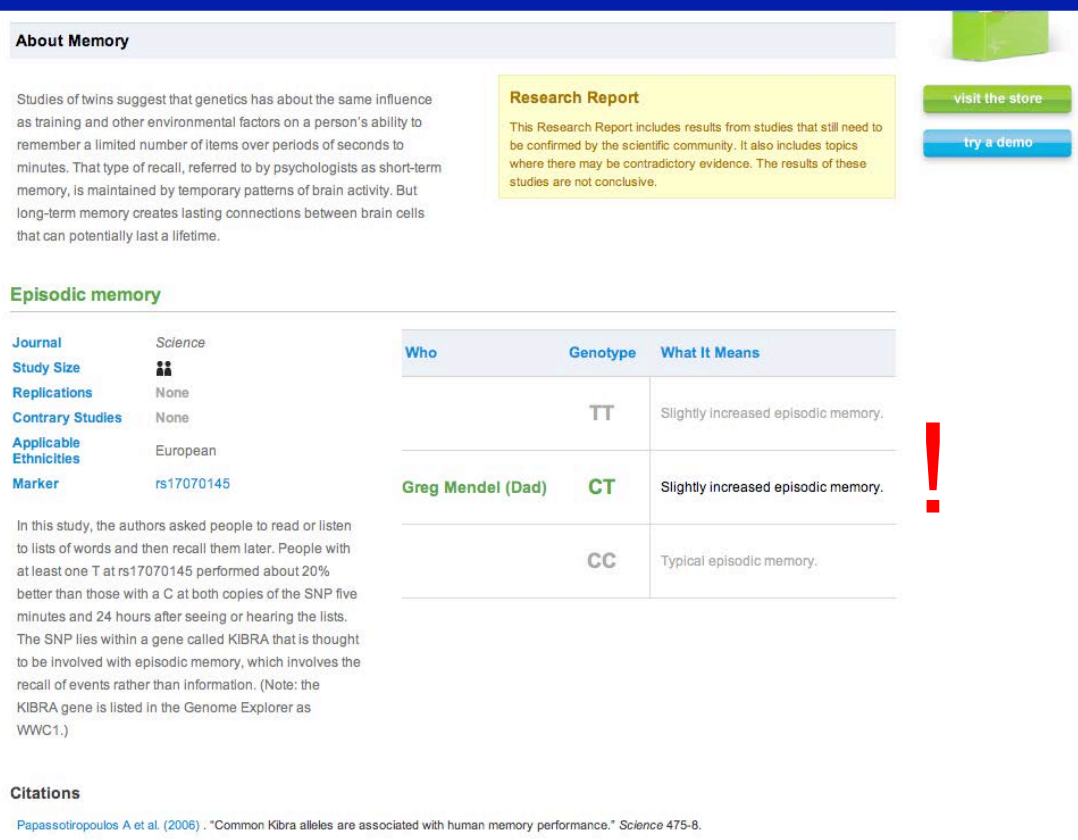
# Personalized medicine?




# 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.

visit the store

try a demo

**Episodic memory**

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

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

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.)

**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*

| | | No. of words recalled | | |
|---|---|---|---|---|
| | *n* | 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§ |

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

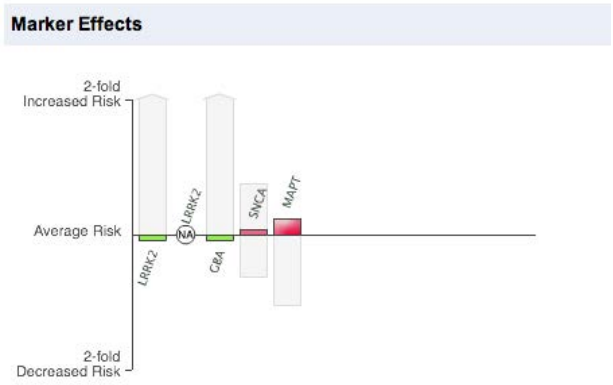
Papassotiropoulos et al. *Science, 2006*

## Wichtigkeit der humangenetischen Forschung

# Falsche Schlüsse vermeiden!

ODER: Addiere nie populations-basierte Risiken um individuelle “Vorhersagen” zu machen!
*(…auch schwer zu vermitteln)*

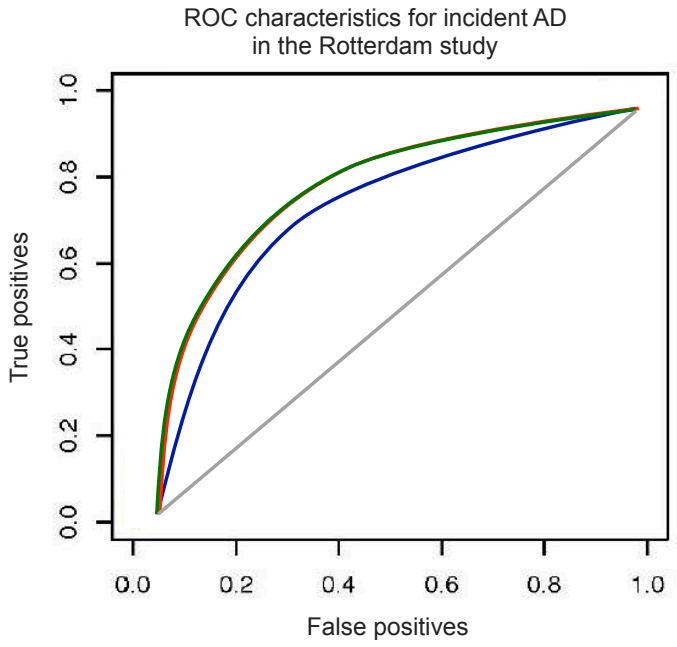
## Individual risk assessment




- 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**

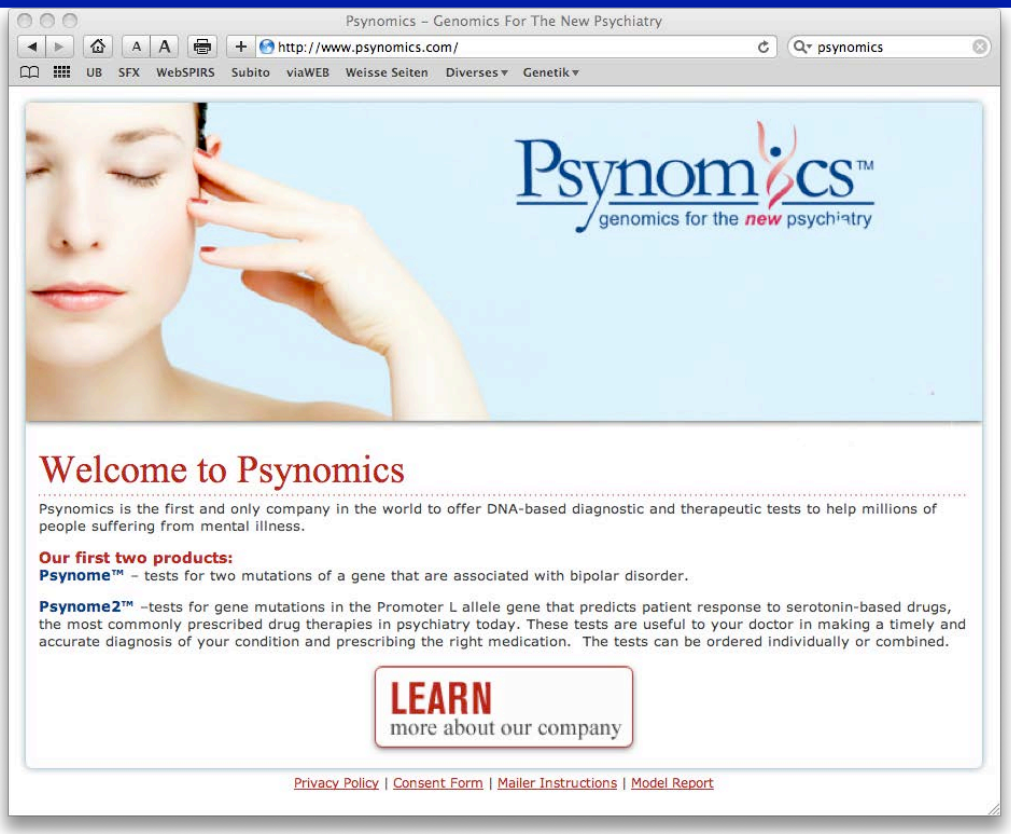
**Background** Comparison of patients with coronary heart disease and controls in genome-wide association studies has revealed several single nucleotide polymorphisms (SNPs) associated with coronary heart disease. We aimed to establish the external validity of these findings and to obtain more precise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



# Personalized medicine?


# Personalized medicine?

**Article**

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


Gonzalo Laje, M.D.

Silvia Paddock, Ph.D.

Husseini Manji, M.D.

A. John Rush, M.D.

Alexander F. Wilson, Ph.D.

Dennis Charney, M.D.

Francis J. McMahon, M.D.



**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



nature news



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

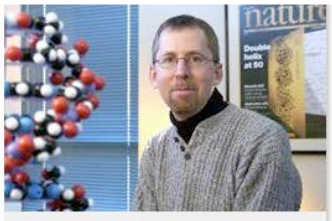
News

## 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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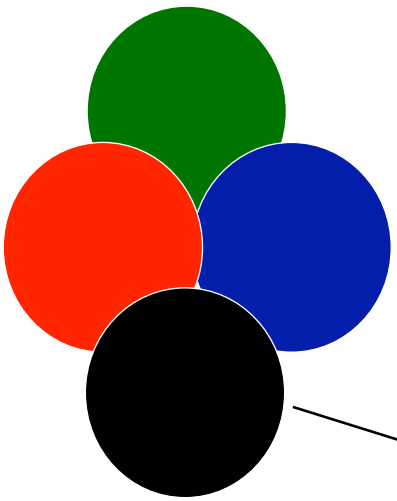
## Personalized medicine

***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?

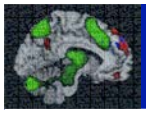


Prediction?

Diagnosis?

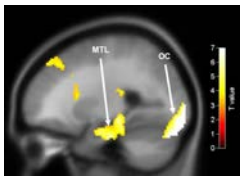
Pharmacogenomics?

Understanding biology!
Identifying new therapeutic possibilities!



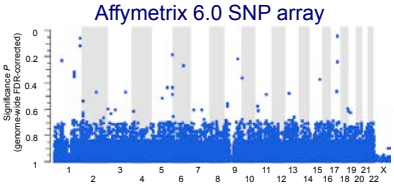
# Current status

memory tasks in health and disease
N > 3000




structural and functional brain imaging
Current N = 600

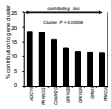
Affymetrix 6.0 SNP array




Clinical trials

single loci

gene/loci groups



computational modeling

biological validation