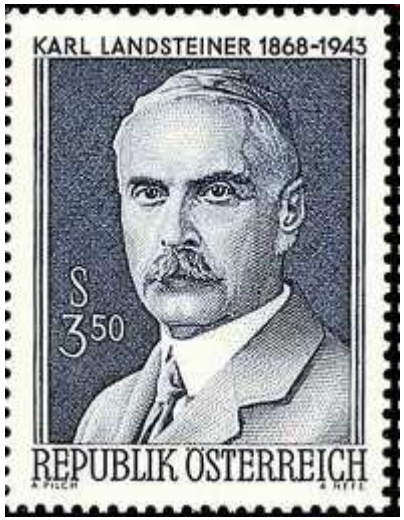
BLUTGRUPPE 0

DELETION

GUANIN 258

GLYCOSYLTRANSFERASE



Identification of *ADAMTS7* as a novel locus for coronary atherosclerosis and association of *ABO* with myocardial infarction in the presence of coronary atherosclerosis: two genome-wide association studies

*Muredach P Reilly, *Mingyao Li, Jing He, Jane F Ferguson, Ioannis M Stylianou, Nehal N Mehta, Mary Susan Burnett, Joseph M Devaney, Christopher W Knouff, John R Thompson, Benjamin D Horne, Alexandre F R Stewart, Themistocles L Assimes, Philipp S Wild, Hooman Allayee, Patrick Linsel Nitschke, Riyaz S Patel, †Myocardial Infarction Genetics Consortium, †Wellcome Trust Case Control Consortium, Nicola Martinelli, Domenico Girelli, Arshed A Quyyumi, Jeffrey L Anderson, Jeanette Erdmann, Alistair S Hall, Heribert Schunkert, Thomas Quertermous, Stefan Blankenberg, Stanley L Hazen, Robert Roberts, Sekar Kathiresan, Nilesh J Samani, Stephen E Epstein, Daniel J Rader

The ABO association was attributable to the glycotransferase-deficient enzyme that encodes the ABO blood group O phenotype previously proposed to protect against myocardial infarction.

Novel Association of ABO Histo-Blood Group Antigen with Soluble ICAM-1: Results of a Genome-Wide Association Study of 6,578 Women

Guillaume Paré[1,2]*, Daniel I. Chasman[1,2], Mark Kellogg[3], Robert Y. L. Zee[1,2], Nader Rifai[3], Sunita Badola[4], Joseph P. Miletich[4], Paul M. Ridker[1,2]

ABO histo-blood group phenotype has been linked to a plethora of diseases, including infectious diseases, cancers and vascular diseases. Particularly interesting is the association of non-O histo-blood groups — and group A in particular — with a higher risk of myocardial infarction, peripheral vascular disease, strokes and venous thromboembolism (MIM 188050). While this phenomenon is partially explained by higher concentrations of the coagulation factors vonWillebrand and VIII (presumably because of decreased clearance), the exact mechanism is not entirely understood. Underlining the complex nature of the biological processes involved, the A1 group (rs507666) is associated with higher levels of sICAM-1, a (positive) predictor of vascular diseases in epidemiological studies.

Journal of Thrombosis and Haemostasis, **6**: 62–69

ORIGINAL ARTICLE

ABO(H) blood groups and vascular disease: a systematic review and meta-analysis

O. WU,* N. BAYOUMI,† M. A. VICKERS† and P. CLARK‡

This study confirms the historical impression of linkage between some vascular disorders and non-O blood group status. Although the odds ratios are similar to those predicted by the effect of ABO(H) on von Willebrand factor levels, further work is required to assess risk prospectively and to refine the effect of reducing O(H) antigen expression on thrombosis.

However, as non-O and particularly A1A1, A1B, BB constitute a significant proportion of the population attributable fraction of VTE, there may be a role for more widespread adoption of ABO(H) typing in testing strategies.

Journal of Thrombosis and Haemostasis, **6**: 62–69

Human Molecular Genetics, 2010, Vol. 19, No. 9 **1863–1872**
doi:10.1093/hmg/ddq061
Advance Access published on February 18, 2010

Large-scale genomic studies reveal central role of ABO in sP-selectin and sICAM-1 levels

Maja Barbalic[1,*,†], Josée Dupuis[3,4,†], Abbas Dehghan[6,8,†], Joshua C. Bis[9,†], Ron C. Hoogeveen[13,†], Renate B. Schnabel[3,†], Vijay Nambi[13], Monique Bretler[6,8], Nicholas L. Smith[10,14], Annette Peters[15], Chen Lu[4], Russell P. Tracy[16,17], Nena Aleksic[13], Jan Heeriga[6,8], John F. Keaney Jr[3], Kenneth Rice[11], Gregory Y.H. Lip[18], Ramachandran S. Vasan[3], Nicole L. Glazer[9], Martin G. Larson[3], Andre G. Uitterlinden[7,8], Jennifer Yamamoto[3], Peter Durda[16], Talin Haritunians[19], Bruce M. Psaty[9,10,12,20], Eric Boerwinkle[1,2], Albert Hofman[6,8], Wolfgang Koenig[21,†], Nancy S. Jenny[16,†], Jacqueline C. Witteman[6,8,†], Christie Ballantyne[13,†] and Emelia J. Benjamin[3,5,22,†]

Also of special interest, group A antigen carriers have been recognized as having a higher risk of suffering from severe malaria when infected by Plasmodium falciparum. Plamodium infected erythrocytes express a receptor (PfEMP-1) that binds specifically to cell-surface group A and B antigen as well as ICAM-1, a major step in the sequestration of infected erythrocytes leading to the clinical complications of severe and cerebral malaria.

Genome-Wide Association Identifies the ABO Blood Group as a Major Locus Associated With Serum Levels of Soluble E-Selectin

Andrew D. Paterson, Maria F. Lopes-Virella, Daryl Waggott, Andrew P. Boright, S. Mohsen Hosseini, Rickey E. Carter, Enqing Shen, Lucia Mirea, Bhupinder Bharaj, Lei Sun, Shelley B. Bull, and the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group*

Arterioscler Thromb Vasc Biol. 2009;29:1958-1967.

Levels of E-selectin were higher in O/O than O/A heterozygotes, which were likewise higher than A/A genotypes. Analysis of subgroups of A alleles reveals heterogeneity in the association, and even after this was accounted for, an intron 1 SNP remained significantly associated. We replicate the ABO association in nondiabetic individuals.

Arterioscler Thromb Vasc Biol. 2009;29:1958-1967.

Human Molecular Genetics, 2010, Vol. 19, No. 9 **1856–1862**
doi:10.1093/hmg/ddq057
Advance Access published on February 10, 2010

Genetic variants in *ABO* blood group region, plasma soluble E-selectin levels and risk of type 2 diabetes

Lu Qi[1,3,*], Marilyn C. Cornelis[1], Peter Kraft[3], Majken Jensen[1], Rob M. van Dam[1,2,3], Qi Sun[1], Cynthia J. Girman[4], Cathy C. Laurie[5], Daniel B. Mirel[6], David J. Hunter[2,3], Eric Rimm[1,2,3] and Frank B. Hu[1,2,3]

In conclusion, by examining a GWA scan, we confirmed that the ABO locus was a major determinant for plasma sE-selectin levels. We found that the variants at ABO locus and the genetic-inferred ABO blood groups were associated with the risk of type 2 diabetes, independent of sE-selectin levels. We found that blood group B was associated with a decreased risk compared with blood group O. The mechanism underlying the observed association remains unknown and our findings warrant the need for further replications in other ethnic groups and functional investigations.

Human Molecular Genetics, 2010, Vol. 19, No. 9

Die **Blutgruppendiät** des amerikanischen Naturheilkundlers Peter J. D'Adamo, geht davon aus, dass Menschen mit unterschiedlichen Blutgruppen Nahrung unterschiedlich verarbeiten. Dafür sollen bestimmte komplexe Glykoproteine in der Nahrung verantwortlich sein, die als Lektine bekannt sind und die bestimmten Blutgruppenmerkmalen (Membranproteinen der roten Blutkörperchen) ähneln. Werden die aus Sicht der Blutgruppendiät „falschen" Lektine mit agglutinierender Wirkung aufgenommen, kann es nach dieser Theorie zur Verklumpung der Antigene im Blut kommen und zahlreiche Krankheiten seien langfristig die Folge. Eine "richtige" Ernährung könne dagegen anhand eines niedrigen Indikanwertes nachgewiesen werden. Diese Theorie sind lt. DGE wissenschaftlich nicht haltbar [2] und die Diät gilt als ungesund

Laut Peter D’Adamo soll die Blutgruppe 0 die älteste Blutgruppe sein. Sie entwickelte sich schon, als die Menschen noch Jäger und Sammler waren. Daher seien Menschen mit Blutgruppe 0 laut der Blutgruppendiät an fleischreiche Nahrung gewöhnt, nicht aber an Getreide oder Milchprodukte, da es zu dieser Zeit weder Ackerbau noch Viehzucht gab. So sollen also Menschen mit Blutgruppe 0 auch heute täglich Fleisch essen, um gesund zu bleiben, und auf Getreide, vor allem auf Weizen sowie auf Milch verzichten. Welche Blutgruppe die älteste „Urblutgruppe“ ist, ist wissenschaftlich nicht nachgewiesen. In der Diskussion sind sowohl Blutgruppe A als auch Blutgruppe 0. Da Menschenaffen ebenfalls die Blutgruppen 0, A und B haben, gilt als gesichert, dass die Blutgruppen nichts mit menschlichen Wirtschaftsformen zu tun haben

Die Blutgruppe A entstand laut D'Adamo mit den ersten Bauern. Sie sollen vor allem Gemüse und Getreide essen, aber kein Fleisch und keine Milch, da die ersten Bauern angeblich keine Tiere zur Nahrungserzeugung hielten. Die Blutgruppe B soll sich unter Viehzüchtern in Asien entwickelt haben, dem „Nomaden-Typ", daher seien Menschen mit Blutgruppe B an Milch gewöhnt, auch bestimmte Fleisch- und Getreidesorten sollen zu ihrer natürlichen Nahrung gehören. Die Blutgruppe AB entstand in jüngerer Zeit aus der Vermischung der Blutgruppen A und B und symbolisiert den modernen Menschen. Diese Gruppe sollte vor allem Obst und Gemüse essen.

nature Vol 461|8 October 2009

OPINION

An agenda for personalized medicine

Pauline C. Ng, **Sarah S. Murray**, **Samuel Levy** and **J. Craig Venter** find differences in results from two direct-to-consumer genetics-testing companies. They therefore give nine recommendations to improve predictions.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Direct-to-Consumer Genomewide Profiling to Assess Disease Risk

Cinnamon S. Bloss, Ph.D., Nicholas J. Schork, Ph.D., and Eric J. Topol, M.D.

A recent survey showed that only 10% of physicians thought they had the necessary training and knowledge in genomics to use genetic testing in treating patients.

THE LANCET

The Lancet, Volume 377, Issue 9770, Page 967, 19 March 2011
doi:10.1016/S0140-6736(11)60367-X

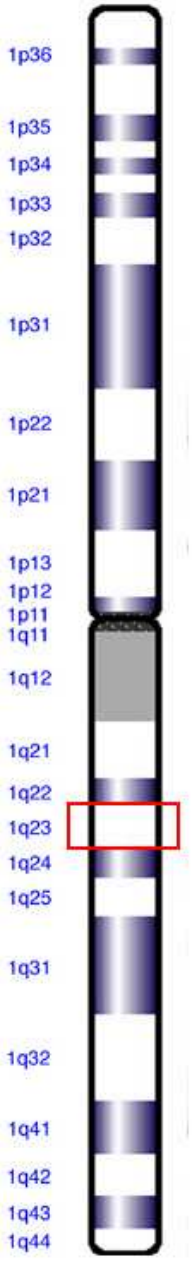
Physicians as guardians of genetic knowledge

Are doctors prepared for the increasing use of genetics in clinical care? Some evidence suggests not. A 2009 survey of more than 10 000 US hysicians by the American Medical Association showed that only 26% had any type of education in the use of genetic testing to guide treatment decisions.

Common susceptibility alleles are unlikely to contribute as strongly as the *FV* and *ABO* loci to VTE risk: results from a GWAS approach

David-Alexandre Trégouët,[1,2] Simon Heath,[3] Noémie Saut,[4] Christine Biron-Andreani,[5] Jean-François Schved,[5] Gilles Pernod,[6] Pilar Galan,[7] Ludovic Drouet,[1,2] Diana Zelenika,[3] Irène Juhan-Vague,[4] Marie-Christine Alessi,[4] Laurence Tiret,[1,2] Mark Lathrop,[3] Joseph Emmerich,[8] and Pierre-Emmanuel Morange[4]

BLOOD, 21 MAY 2009 • VOLUME 113, NUMBER 21



SYMBOL	rs NCBI	POLYMORPHISMUS
F5	**rs6025**	**Arg506Gln**

Das weithin bekannte F5 Leiden Allel codiert für eine Faktor V Variante, die nur ungenügend durch APC inaktiviert wird. Durch diesen Polymorphismus kann der Antagonist des Faktor V, nämlich das aktivierte Protein C nicht angreifen und die Prothrombinwirkung des Faktor V nicht ausbalancieren. Dies ist mit einer höheren Inzidenz thromboembolischer Ereignisse verbunden.

Review

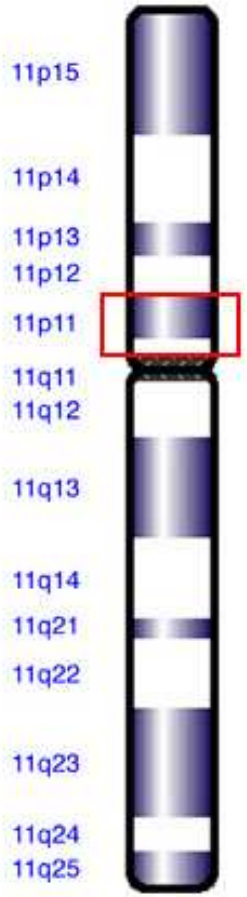
Factor V Leiden, prothrombin G20210A substitution and hormone therapy: indications for molecular screening

Maria Grazia Andreassi[1,*], Nicoletta Botto[1] and Silvia Maffei[2]

Clin Chem Lab Med 2006;44(5):514–521

the risk of VTE associated with OC is 10- to 35-fold higher among factor V Leiden carriers in comparison with the risk among non-carriers and/or non-users The pooled odds ratio estimated by a recent meta-analysis showed a 15.62-fold increased risk

Like OCs, there are also data indicating a 13- to 16-fold increased risk of VTE during HRT among women with factor V Leider Furthermore, women with factor V Leiden have a substantially increased risk of myocardial infarction or stroke on HRT compared to women without this mutation on HRT



SYMBOL	rs NCBI	POLYMORPHISMUS
F2	**rs1799963**	**G/A Pos. 20210**

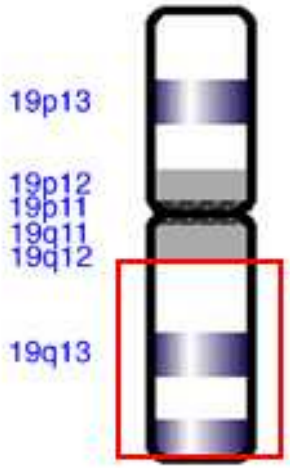
Das humane Prothrombin Gen (F2) besitzt einen vorkommenden Polymorphismus (G/A Pos. 20210) innerhalb der 3'-untranslatierten Region, der zu erhöhten Serum Prothrombin - Spiegeln und somit zu einer erhöhten Gerinnbarkeit des Blutes führt.

Recently, the Estrogen and Thromboembolism Risk (ESTHER) study confirmed associations between increased VTE risk in postmenopausal women and current use of oral estrogen or the presence of either factor V Leiden or prothrombin G20210A mutations

In women who both carry a prothrombotic mutation and use oral estrogen, VTE risk is 25-fold increased compared with non-users without mutation.

In addition, several studies have also found an association between the presence of prothrombin G20210A polymorphism and the risk of myocardial infarction or stroke in women on HRT who were also carriers of the allele A compared with the wild-type genotype

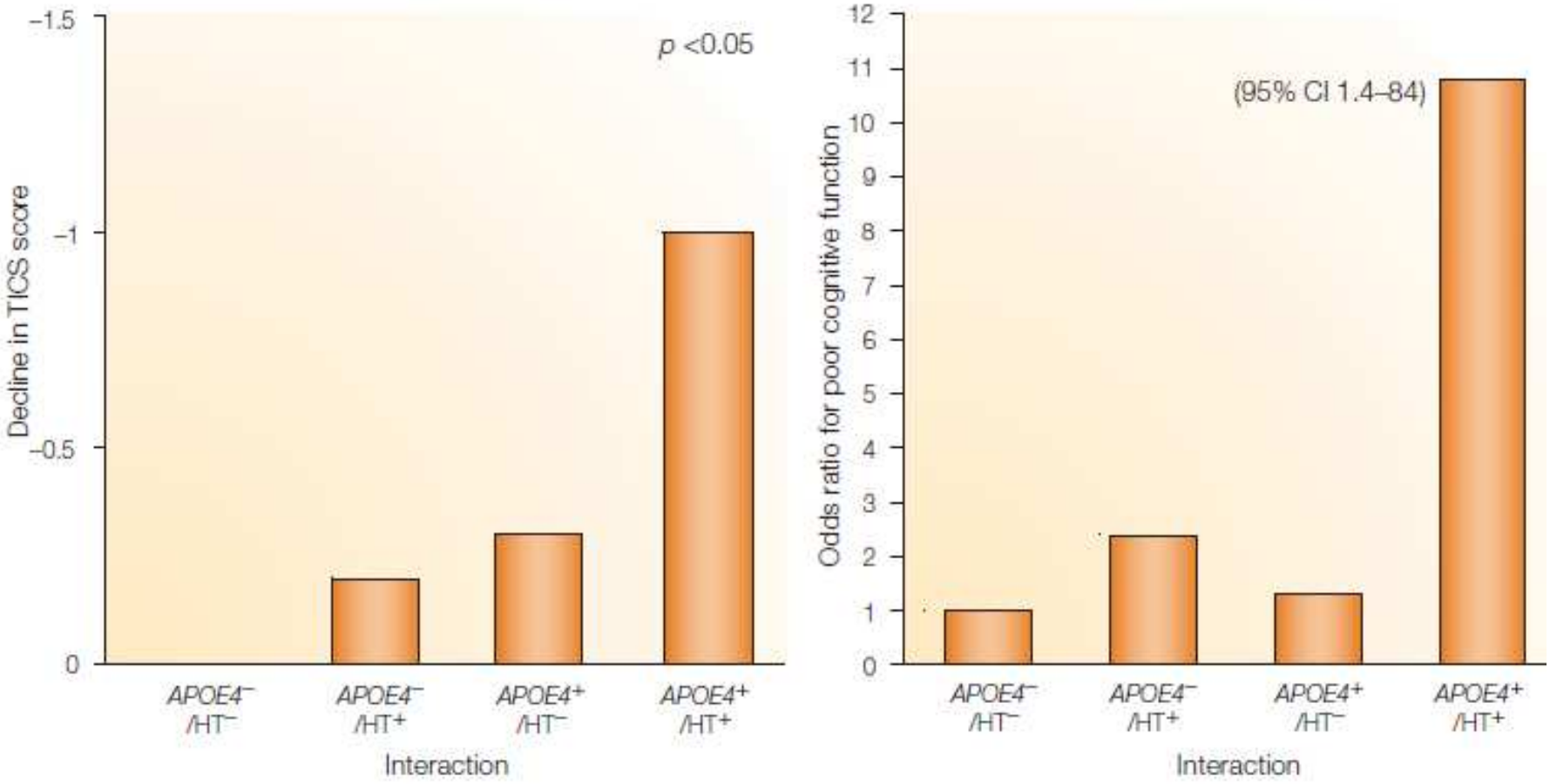
SYMBOL	rs NCBI	POLYMORPHISMUS
APOE	rs429358	Cys112Arg
APOE	rs7412	Arg158Cys



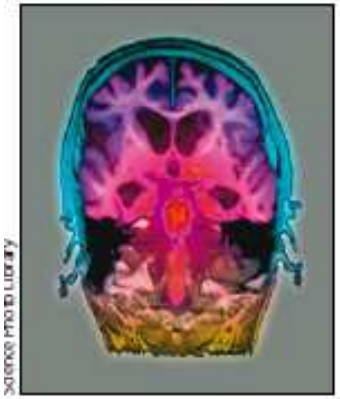
Das APOE-Protein besteht aus 299 Aminosäuren mit einer wichtigen Bindungsstelle zwischen den Aminosäuren 140 und 160. Das auf Chromosom 19 lokalisierte APOE-Gen kommt in drei bekannten Allelvarianten (e2, e3 und e4) vor, die wiederum drei Isoformen des Proteins bilden:
E2, E3 und E4.

APOE3 ist die häufigste Isoform und besitzt ein Cystein in Aminosäure Position 112 und innerhalb der Bindungsregion ein Arginin in Aminosäure Position 158. APOE4 besitzt ein Arginin an Stelle 112 und hat normale Bindungskapazität. APOE2 trägt ein Cystein in der Bindungsregion an Stelle 158 und zeigt nur 1-2 % der normalen Bindungskapazität

Untreated hypertension, *APOE4* carriers and risk of cogitive impairment



Why are drug trials in Alzheimer's disease failing?



Last week, semagacestat added itself to the phase 3 scrapheap of other disease-modifying hopefuls for Alzheimer's disease. This drug is a γ-secretase inhibitor of the final step in amyloid-β protein synthesis, aggregates of which form plaques, the hallmark of the disease.

A recent review in *The Lancet Neurology* summarises the problems for drug development in Alzheimer's disease. Other drugs also failed phase 3 trials. Hopes were high for latrepirdine, but its CONNECTION study did not reveal

Another meta-analysis showed tha
significant animal studies are less like
such publication bias can overestimat

Current treatment targets patients
Alzheimer's disease. But perhaps th
treated too late, when damage is irr
time to treat Alzheimer's disease is
memory loss and tissue destruction
hard to model in animals. That means

Alzheimer's disease: clinical trials and drug development

Francesca Mangialasche, Alina Solomon, Bengt Winblad, Patrizia Mecocci, Miia Kivipelto

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Disclosure of *APOE* Genotype for Risk of Alzheimer's Disease

Robert C. Green, M.D., M.P.H., J. Scott Roberts, Ph.D., L. Adrienne Cupples, Ph.D., Norman R. Relkin, M.D., Ph.D., Peter J. Whitehouse, M.D., Ph.D., Tamsen Brown, M.S., Susan LaRusse Eckert, M.S., Melissa Butson, Sc.M., A. Dessa Sadovnick, Ph.D., Kimberly A. Quaid, Ph.D., Clara Chen, M.H.S., Robert Cook-Deegan, M.D., and Lindsay A. Farrer, Ph.D., for the REVEAL Study Group*

CONCLUSIONS

The disclosure of *APOE* genotyping results to adult children of patients with Alzheimer's disease did not result in significant short-term psychological risks. Test-related distress was reduced among those who learned that they were *APOE* ε4–negative. Persons with high levels of emotional distress before undergoing genetic testing were more likely to have emotional difficulties after disclosure. (ClinicalTrials.gov number, NCT00571025.)

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

DRUG THERAPY

Alastair J.J. Wood, M.D., *Editor*

Pharmacogenomics — Drug Disposition, Drug Targets, and Side Effects

William E. Evans, Pharm.D., and Howard L. McLeod, Pharm.D.

Modulation of cytochrome P450 activity: implications for cancer therapy

Charity D Scripture, Alex Sparreboom, William D Figg

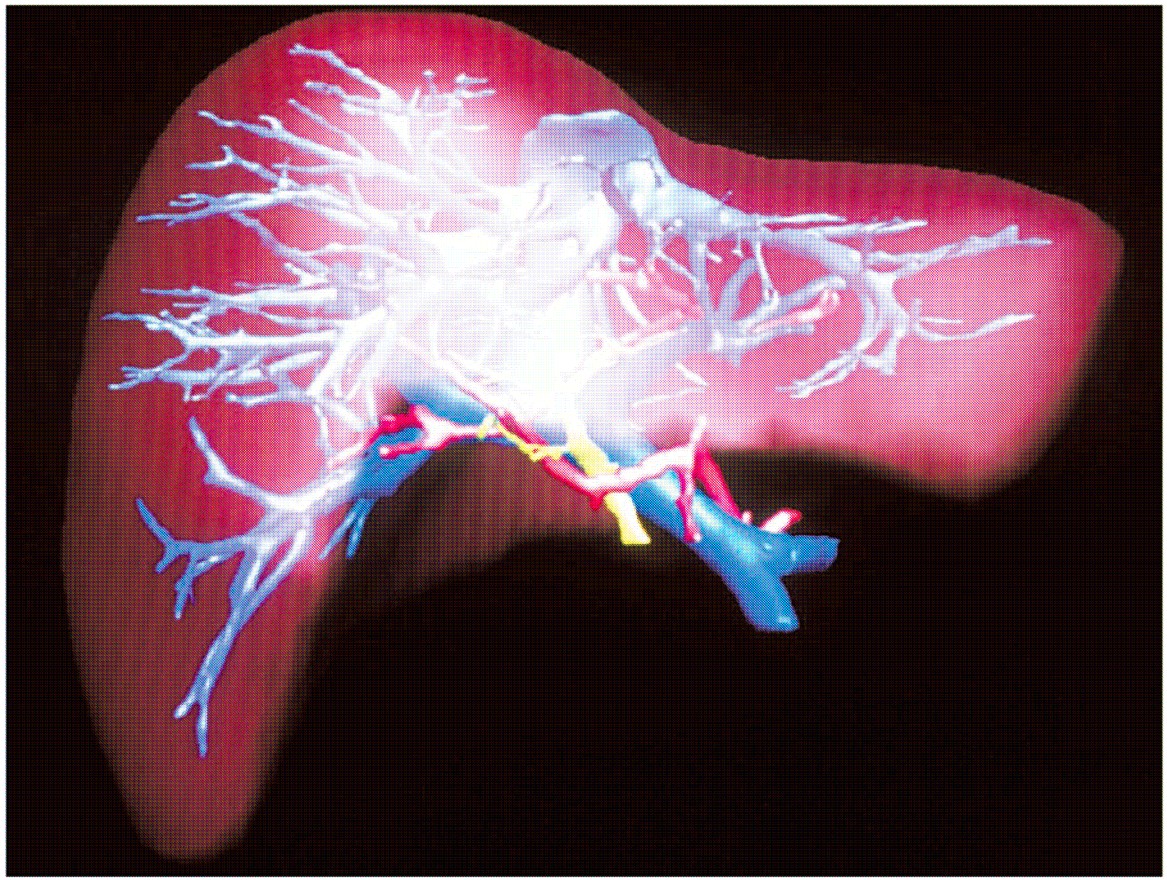


Figure 1: Cytochrome P450 mediates metabolism of drugs in the liver

Lancet Oncology 2005; 6(10):780-789.

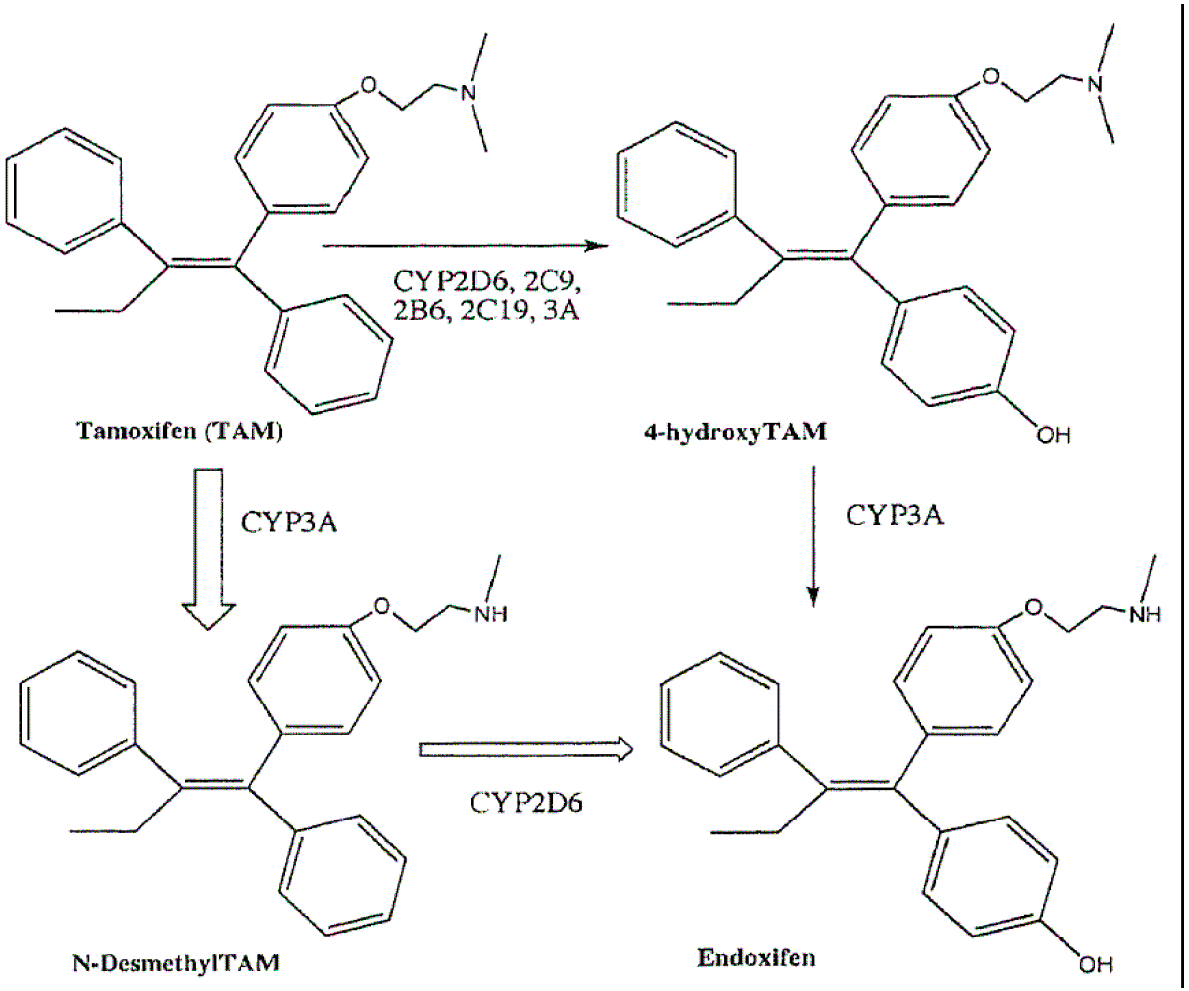

CTRC–AACR
San Antonio
Breast Cancer
Symposium
December 10-14, 2008
Henry B. Gonzalez Convention Center, San Antonio, Texas, USA

CYP2D6 Polymorphisms and the Impact on Tamoxifen Therapy

JACOB N. BEVERAGE,[1] TRISTAN M. SISSUNG,[1] AMY M. SION,[1] ROMANO DANESI,[2] WILLIAM D. FIGG[1]

[1]Clinical Pharmacology Research Core, Medical Oncology Branch, Center for Cancer Research, National Cancer Institute, 9000 Rockville Pike, Building 10, Room 5A01, Bethesda, Maryland

[2]Department of Oncology, Transplants and Advanced Technologies in Medicine, University of Pisa, Pisa, Italy



To further explore the potential relationship between deficiencies in the CYP2D6 gene and outcomes achieved with tamoxifen among women with hormone-positive breast cancer, researchers from the Mayo Clinic conducted a retrospective analysis of a subgroup of patients from the Austrian Breast and Colorectal Study Group-8 (ABCSG-8) trial. The ABCSG-8 was a prospective clinical trial conducted between 1996-2004 in which 3,901 women with hormone-positive breast cancer were randomized prior to treatment to two years of adjuvant tamoxifen followed by three years of Arimidex® (anastrozole) or five years of adjuvant tamoxifen.

* At five years poor metabolizers who were randomized to tamoxifen had a 3.8-fold increased risk of recurrence compared with extensive metabolizers of tamoxifen.

* However, poor metabolizers who were randomized to switch to Arimidex after two years of tamoxifen did not experience an increased recurrence risk at years three and five.

The researchers concluded that these results provide further evidence that testing for CYP2D6 variances can help determine which patients may respond to tamoxifen and that testing prior to adjuvant therapy should be considered following discussion with the patient.

Reference: Goetz M, Ames M, Gnant M et al. Pharmacogenetic (CYP2D6) and gene express profiles (HOXB13/IL17BR and molecular grade index) for prediction of adjuvant endocrine therapy benefit in the ABCSG 8 trial. Presented at the San Antonio Breast Cancer Symposium. December 13, 2008. Abstract 57

CYP2D6 Gene Variants May Affect Responses to Tamoxifen Among Breast Cancer Patients

By CancerConsultants.com

January 5, 2009

CYP2D6 Gene Variants May Affect Responses to Tamoxifen Among Breast Cancer Patients

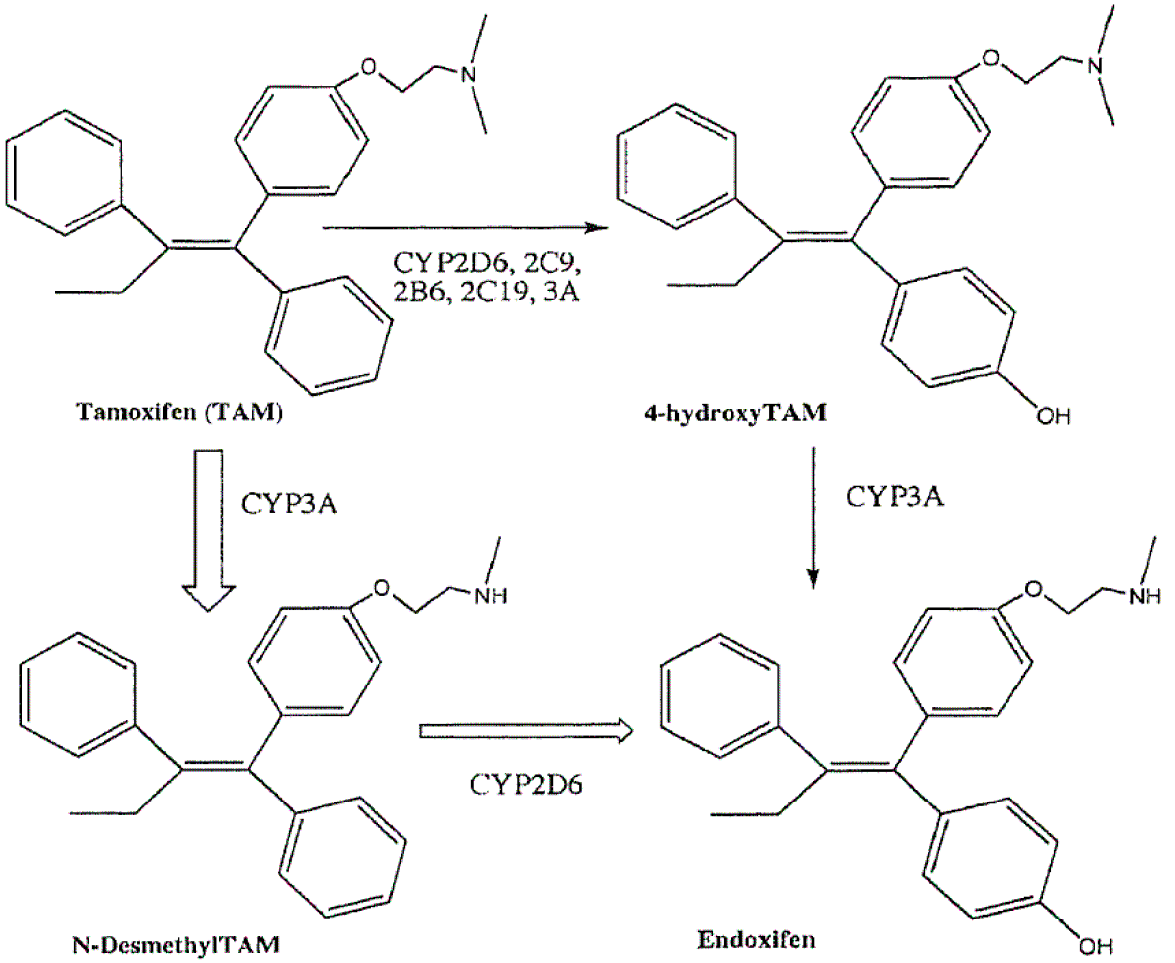
Among postmenopausal women with estrogen receptor-positive breast cancer, those with certain variations in the CYP2D6 gene derived little benefit from tamoxifen (Nolvadex®); based on these findings, researchers at the Mayo Clinic recommend CYP2D6 testing for postmenopausal women being considered for adjuvant tamoxifen therapy. These results were presented at the 2008 San Antonio Breast Cancer Symposium

CYP2D6 Polymorphisms and the Impact on Tamoxifen Therapy

JACOB N. BEVERAGE,[1] TRISTAN M. SISSUNG,[1] AMY M. SION,[1] ROMANO DANESI,[2] WILLIAM D. FIGG[1]

[1]Clinical Pharmacology Research Core, Medical Oncology Branch, Center for Cancer Research, National Cancer Institute, 9000 Rockville Pike, Building 10, Room 5A01, Bethesda, Maryland

[2]Department of Oncology, Transplants and Advanced Technologies in Medicine, University of Pisa, Pisa, Italy



PM poor metaboliser

IM intermediate metaboliser

EM: extensive metaboliser

Substrates

Substrates refers to drugs that are either activated or deactivated by the pathway.
Note=italics indicated minor pathway

Substrates Metabolized through Cytochrome P-450 2D6

acetaminophen
ajmaline
alprenolol
amiflamine
amitriptyline
amphetamine
amprenavir
aprinidine
bisoprolol
brofaramine
bufuralol
bunitrolol
buthylamphetamine
captopril
carteolol
carvedilol
chloropromazine
chlorpheniramine
chlorpyrifos
cinnarizine
citalopram
clomipramine
clozapine
codeine
debrisoquine
delavirdine
desipramine
dexfenfluramine
dextromethorphan
diazonin
dihydrocodeine
diltiazem
diprafenone
disopyramide
dolasetron
donepezil
doxepin
encainide
ethylmorphine
ezlopitant
felbamate
flecainide
flunarizine
fluoxetine
fluperlapine
fluphenazine
fluvoxamine
galantamine
guanoxan
haloperidol
ibogaine
iloperidone
imipramine
indoramin
loratidine
maprotline
mephobarbital
mequitazine
methadone
methamphetamine
methoxyphenamine
metoprolol
mexiletine
mianserin
minaprine
mirtazapine
norcodeine
nortriptyline
olanzapine
ondansetron
oxycodone
parathion
paroxetine
perhexiline
perphenazine
phenformin
procainamide
promethazine
propafenone
propranolol
ranitidine
remoxipride
risperidone
sparteine
tamoxifen
tamsulosin
thioridazine
timolol
tolterodine
tramadol
trimipramine
tropisetron
venlafaxine
verapamil
zotepine
zuclopenthixol

Evidence Report/Technology Assessment

Number 146

Testing for Cytochrome P450 Polymorphisms in Adults With Non-Psychotic Depression Treated With Selective Serotonin Reuptake Inhibitors (SSRIs)

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-02-0025

Prepared by:
Duke Evidence-based Practice Center, Durham, NC

Investigators
David B. Matchar, M.D., Principal Investigator

Pharmacogenomic of SSRI

Review article

CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages

Kirchheiner J, Brøsen K, Dahl ML, Gram LF, Kasper S, Roots I, Sjöqvist F, Spina E, Brockmöller J. CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages.
Acta Psychiatr Scand 2001: 104: 173–192.

J. Kirchheiner[1], K. Brøsen[2], M. L. Dahl[3], L. F. Gram[2], S. Kasper[4], I. Roots[1], F. Sjöqvist[3], E. Spina[5], J. Brockmöller[6]

[1]Institute of Clinical Pharmacology, Charité, Humboldt

SAROTEN AMITRIPTYLIN (AT)

AT → NORTRYPTILIN

↑

CYP 2 C19

CYP 2 D 6

CYP 2 D6 POOR METABOLIZER (PM):

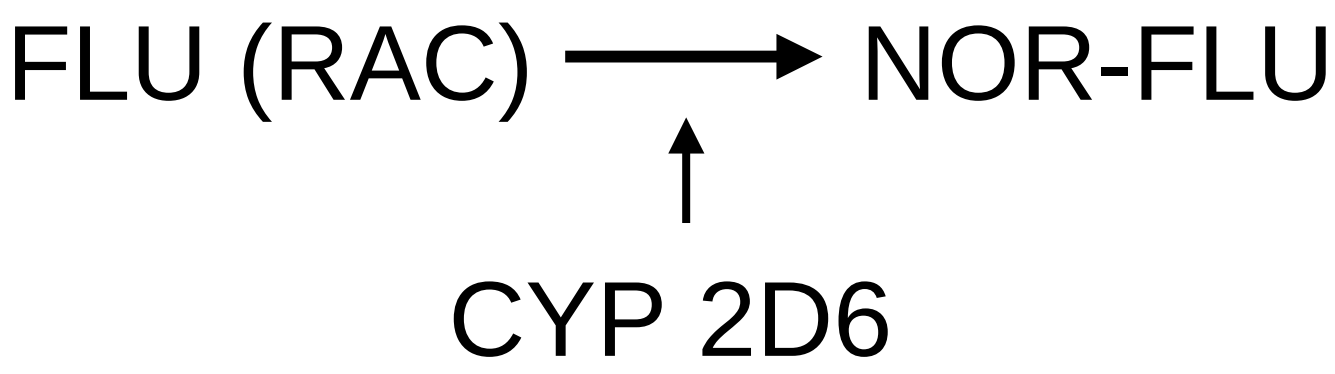
50% recommended dose

CYP 2 D6 EXTENSIVE METABOLIZER (EM):

120% recommended dose


NDC 0406-0663-01
100 CAPSULES
FLUOXETINE
Capsules, USP
Fluoxetine Hydrochloride
Equivalent to
20 mg
Fluoxetine
Rx only
Mallinckrodt

FLUOXETINE (FLU)



PM CYP 2D6 INITIALDOSIS 70%

EM CYP 2D6 INITIALDOSIS 110%

FLUCTIN

SYMBOL	rs NCBI	POLYMORPHISMUS
ACE	**rs4646994**	**Ins/Del Intron 16**

Das menschliche ACE-Gen besitzt einen bekannten Insertions/ Deletions (I/D) Polymorphismus, dessen D/D Genoytp mit hohen Plamaspiegeln des Enzyms und damit verbundenen erhöhten Angiotensin II Konzentrationen assoziiert ist.

Renin Angiotensin System Gene Polymorphisms Modify Angiotensin-Converting Enzyme Inhibitors' Effect on Cognitive Function: The Health, Aging and Body Composition Study

Ihab Hajjar, MD, MS,[*†] *Stephen Kritchevsky, PhD,*[‡] *Anne B. Newman, MD, MPH,*[§] *Rongling Li, MD, PhD, MPH,*[‖] *Kristine Yaffe, MD,*[#] *Eleanor M. Simonsick, PhD,*[**] *and Lewis A. Lipsitz, MD,*[*†] *for the Health, Aging and Body Composition Study*

Therefore, ACE-Is may have nonvascular effects that would lead to further brain and cognitive protection. For example, ACEIs are associated with upregulation of neprilysin, an amyloid beta–degrading enzyme, inhibition of the angiotensin II–related anticholinergic effect and lower levels of inflammatory biomarkers.

Angiotensin II

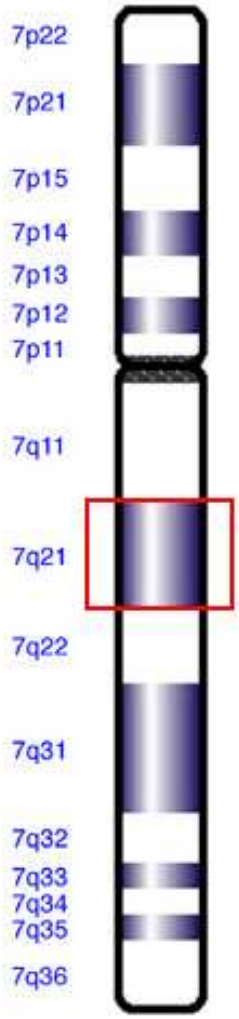
Inflammation ↑

ROS ↑

Symphaticus ↑

Adiponectin ↓

PPARγ ↓

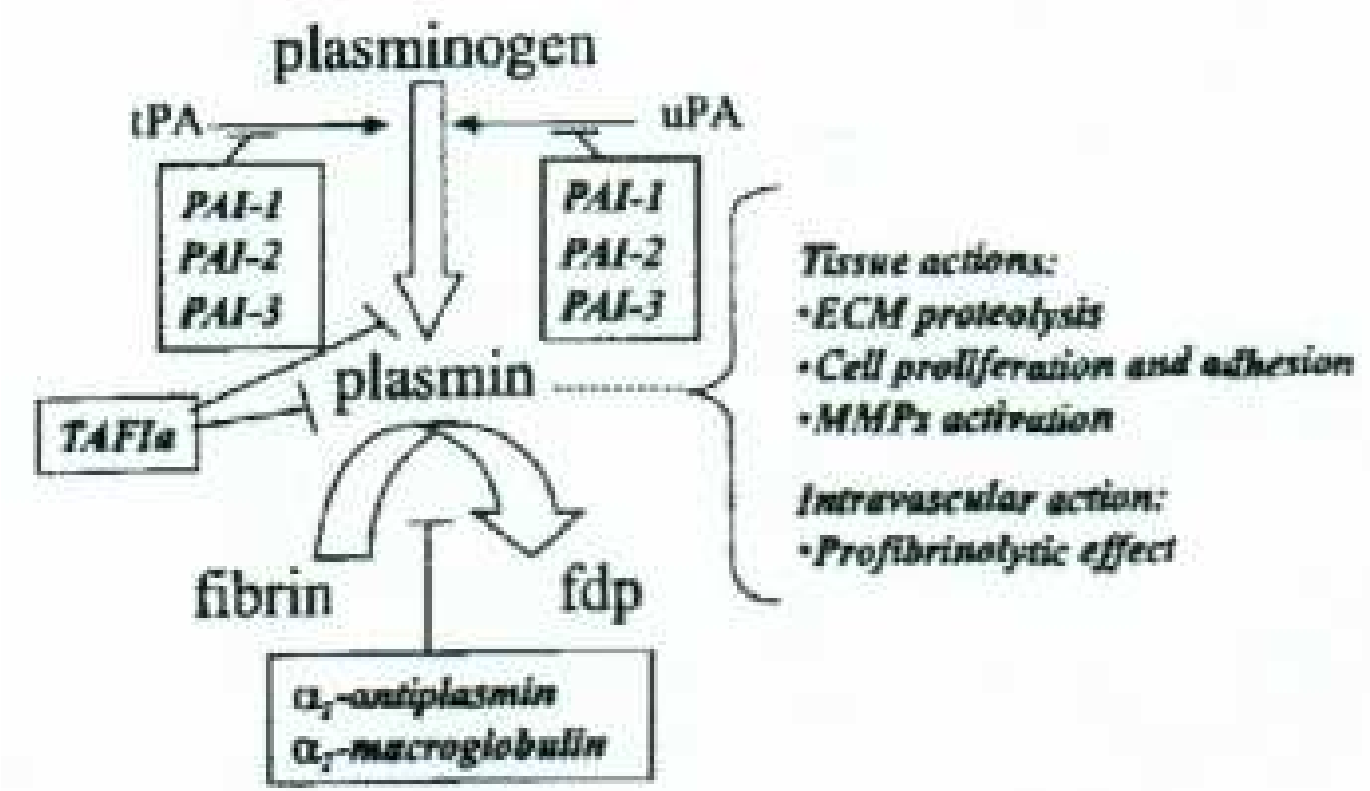


SYMBOL	rs NCBI	POLYMORPHISMUS
PAI1 (SERPINE1)	**n.a.**	**5G/4G Promoter**

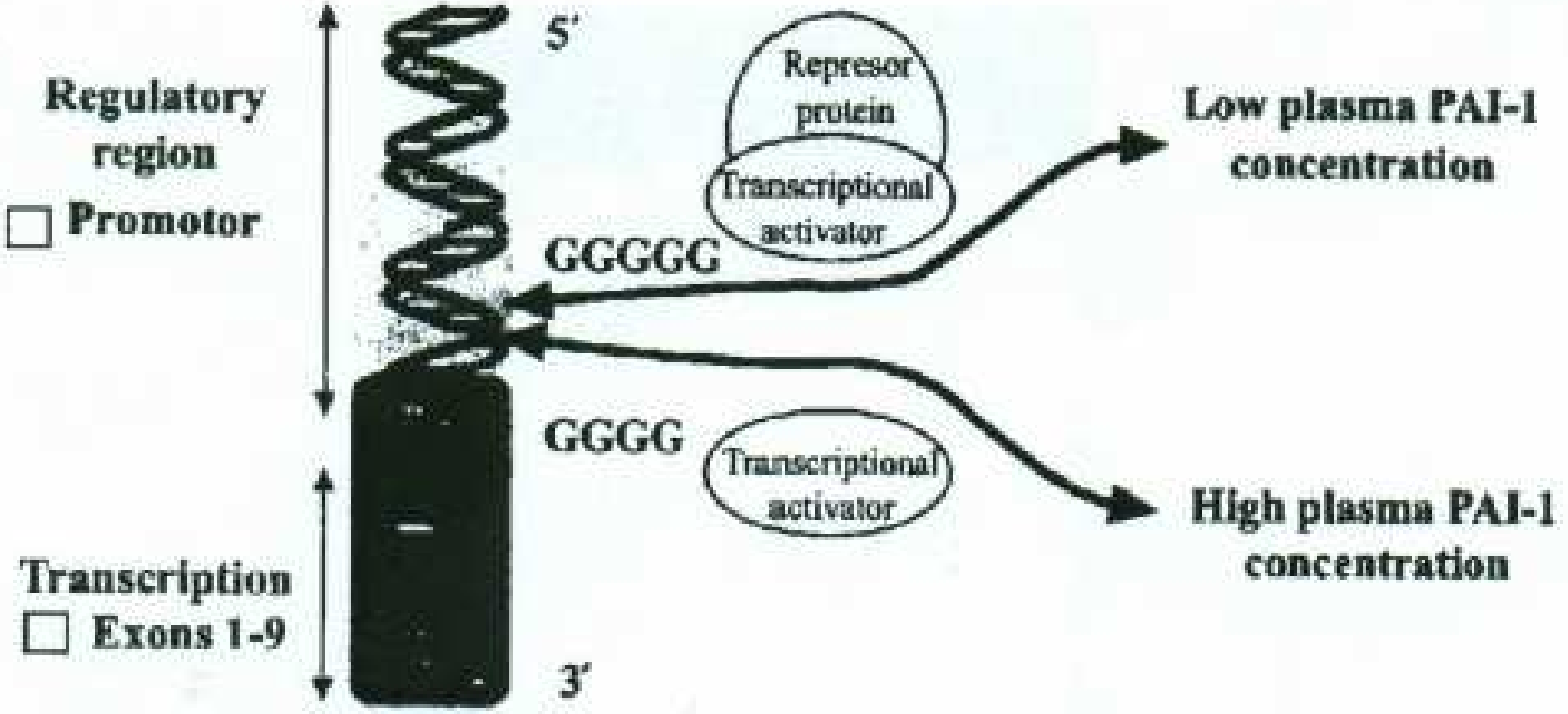
Die Trägerschaft des 4G – Allels ist mit erhöhtem PAI-1 Plasmaspiegel assoziiert.

Fibrinolysis: The Key to New Pathogenetic Mechanisms

Esther Zorio, Juan Gilabert-Estellés, Francisco España, Luis A. Ramón, Raul Cosín and Amparo Estellés*



Current Medicinal Chemistry, 2008, *15*, 923-929

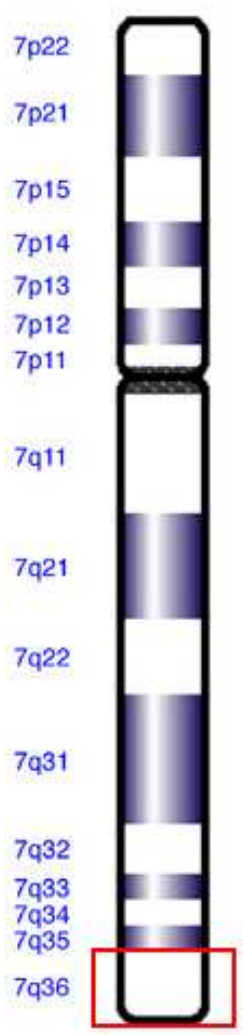


Current Medicinal Chemistry, 2008, *15*, 923-929

PAI SNP

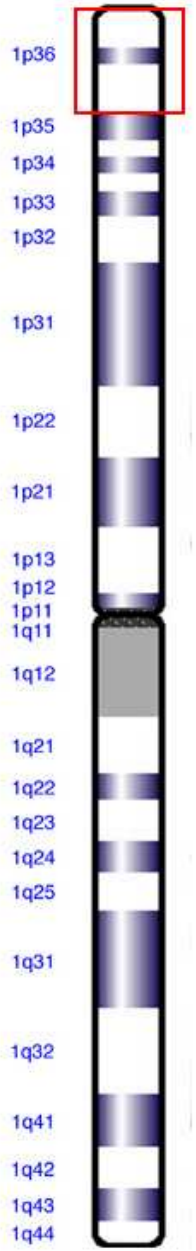
Plasminogen
pro Thrombin
Fibrinogen

PAII	1 - 7 U/ml
F12	69 - 229 pmol/l
FIB/FIBI	180 - 390 mg/dl



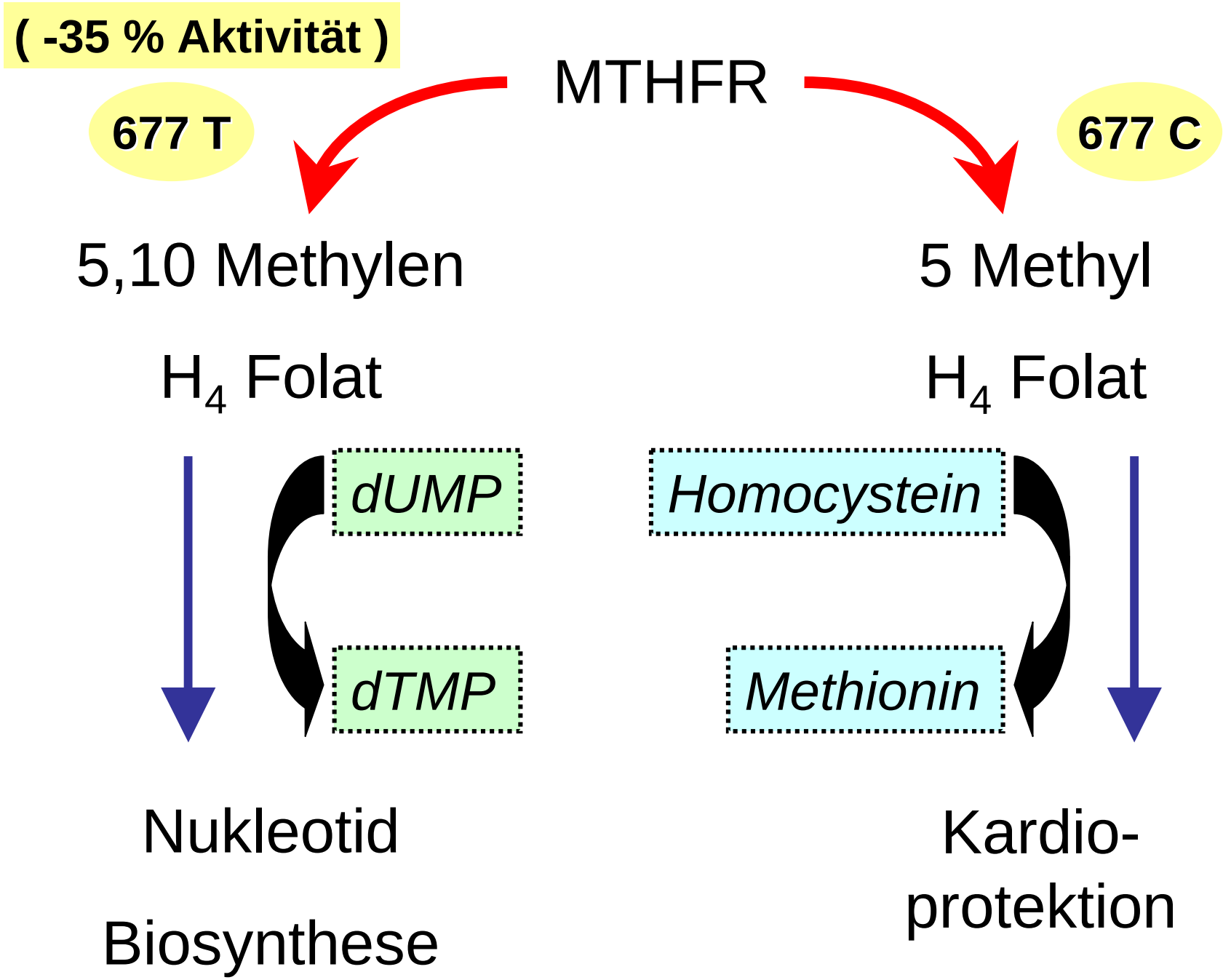
SYMBOL	rs NCBI	POLYMORPHISMUS
NOS3	**rs1799983**	**Glu298Asp**
NOS3	**rs2070744**	**T/C Pos. -786**

Vor allem zwei Polymorphismen gehen mit einer reduzierten
eNOS Aktivität einher, der Glu298Asp Polymorphismus sowie der T/C Pos.-786 Promotorpolymorphismus.



SYMBOL	rs NCBI	POLYMORPHISM
MTHFR	**rs1801133**	**Ala222Val (C/T Pos.677)**

Der C > T Austausch in der Pos. 677 im MTHFR Gen führt zum Aminsäureaustausch Alanin nach Valin. Die Valin-Variante ist mit reduzierter Enzymaktivität und einem moderat erhöhten Homcysteinspiegel verbunden. Homozygote Träger des T-Allels (T/T) haben ein um ca. 25 % höheres tHcy im Vergleich zu homozygoten C-Trägern (C/C).

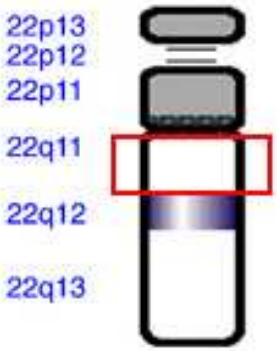

(-35 % Aktivität)
MTHFR
677 T
677 C
5,10 Methylen
H4 Folat
5 Methyl
H4 Folat
dUMP
dTMP
Homocystein
Methionin
Nukleotid
Biosynthese
Kardio-
protektion

Überspielte Wirkung

Folsäure schützt nicht immer vor Infarkten

Dass erhöhte Mengen der Aminosäure Homocystein im Blut die Ausbildung von Herzinfarkten und anderen arteriosklerotisch bedingten Krankheiten begünstigen, legen etliche Beobachtungen nahe. Das Umgekehrte trifft hingegen nicht gleichermaßen zu. So vermag die vermehrte Aufnahme von Folsäure, ein probates Verfahren zur Senkung erhöhter Homocysteinwerte im Blut, die Infarktgefahr nicht immer einzudämmen. Eine Erklärung für dieses rätselhafte Phäno-

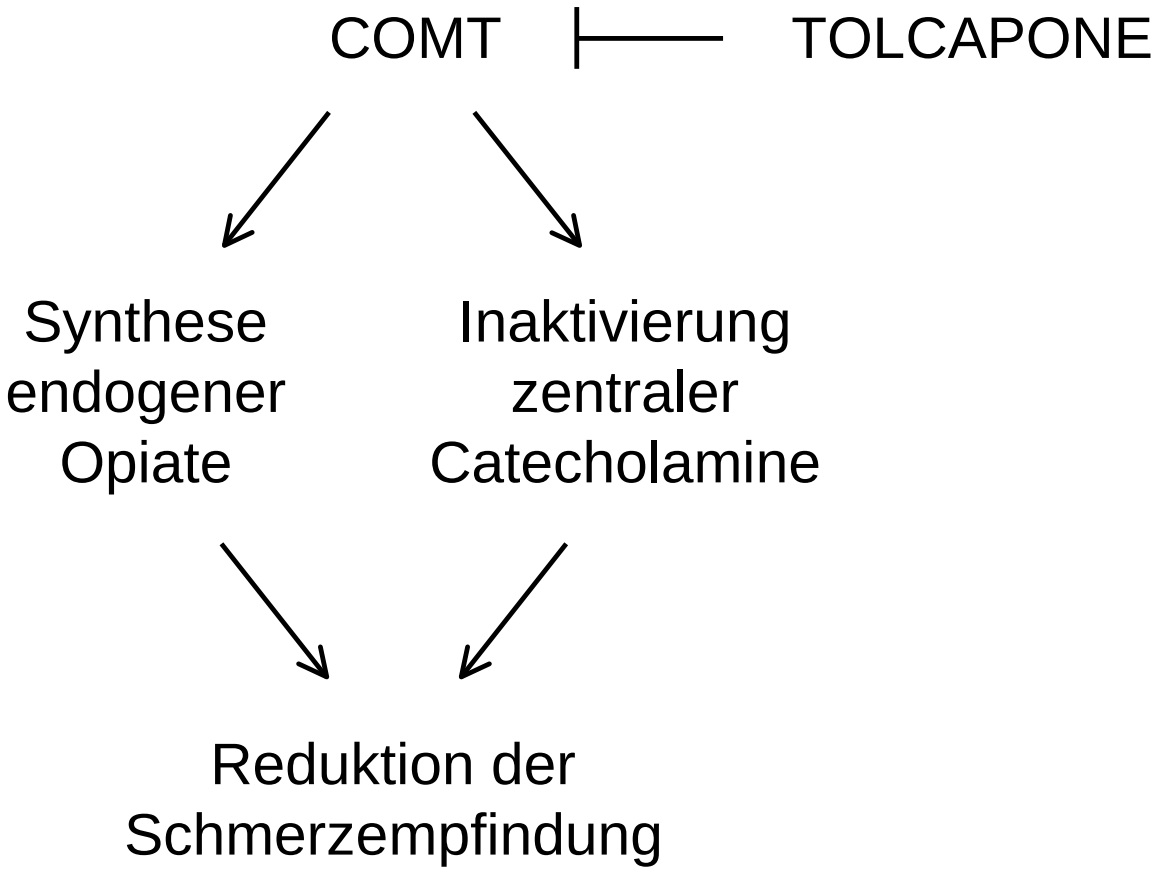
FRANKFURTER ALLGEMEINE ZEITUNG, Nr. 39, 16. Februar 2011

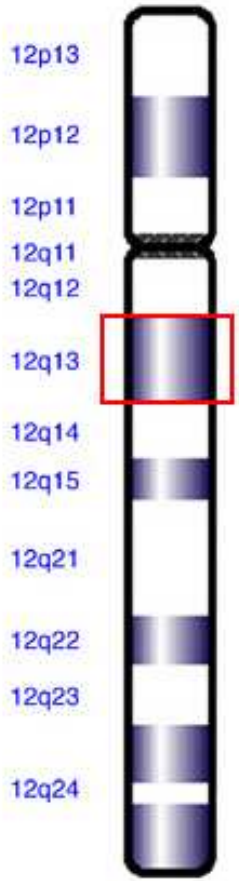


SYMBOL	rs NCBI	POLYMORPHISMUS
COMT	**rs4680**	**Val158Met**

Der sicher am häufigsten untersuchte Polymorphismus im COMT Gen ist die Val158Met Variante (manchmal auch Val>Met Codon 108 genannt). Dieser Basenaustausch ist mit verringerter Enzymaktivität und herabgesetztem Abbau von Östrogenen und anderen Katechol-Verbindungen assoziiert.

SCHMERZEMPFINDUNG





SYMBOL	rs NCBI	POLYMORPHISMUS
VDR	**rs2228570**	**VDR FokI f/F (T/C)**

FokI polymorphism

Dieser Polymorphismus führt zur Bildung von zwei unterschiedlichen VDR Proteinen. Der T nach C Basenaustausch führt durch Veränderung des Translationsstartpunkts zu einem um drei Aminosäuren verkürzten Protein.

Das, durch das so genannte f-Allel kodierte, längere Protein, besitzt schwächere Aktivität als Transkriptionsfaktor für VDR spezifische Zielgene.

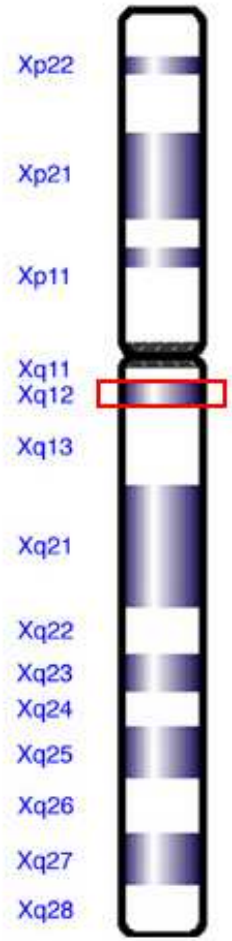
Die kürzere Variante, durch das F bzw. C-Allel kodiert, besitzt im Vergleich zum längeren Protein stärkere Aktivität.

OPEN ACCESS Freely available online PLOS MEDICINE

A Prospective Study of Plasma Vitamin D Metabolites, Vitamin D Receptor Polymorphisms, and Prostate Cancer

Haojie Li[1*], Meir J. Stampfer[1,2,3,4,5], J. Bruce W. Hollis[6], Lorelei A. Mucci[1], J. Michael Gaziano[4,5], David Hunter[1,2,3], Edward L. Giovannucci[1,2,3], Jing Ma[1]

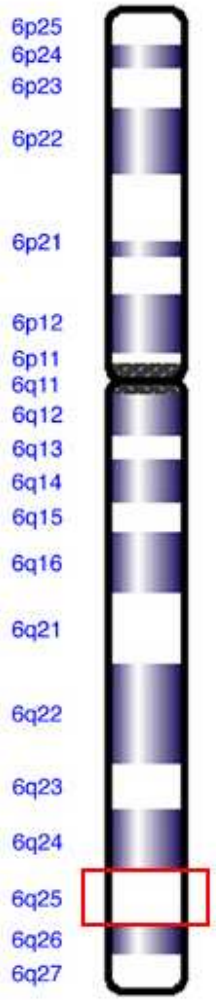
Our data suggest that a large proportion of the US men had uboptimal vitamin D status (especially during the winter/spring season), and both 25(OH)D and 1,25(OH)2D may play an important role in preventing prostate cancer progression. Moreover, vitamin D status, measured by 25(OH)D in plasma, interacts with the VDR FokI polymorphism and modifies prostate cancer risk. Men with the less functional FokI ff genotype (14% in the European-descent population of this cohort) are more susceptible to this cancer in the presence of low 25(OH)D status.



SYMBOL	POLYMORPHISMUS
AR	**(CAG)n short > long alleles**

Im Exon 1 des Androgenrezeptor-Gens (AR) befindet sich ein prominenter polymorpher CAG-Trinucleotide-Repeat-Polymorphismus.

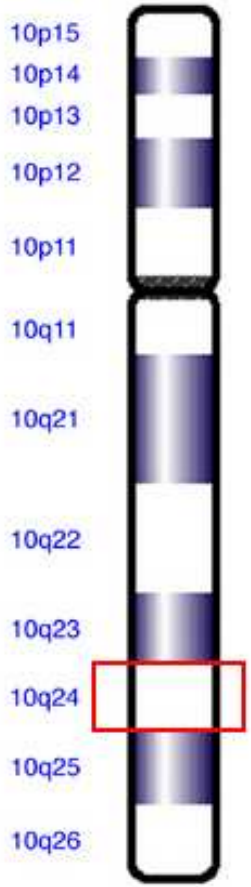
Die polymorphe Anzahl der Wiederholungen der CAG Sequenz im AR Gen beeinflusst die Effizienz des Rezeptors: die Anzahl ist invers mit der Fähigkeit, die Androgenwirkung über den Rezeptor zu vermitteln, assoziiert - Allele mit weniger CAG-Repeats sind aktiver.



SYMBOL	rs NCBI	POLYMORPHISMUS
ESR1	**rs2234693**	**IVS1 -401 T/C (p/P)**

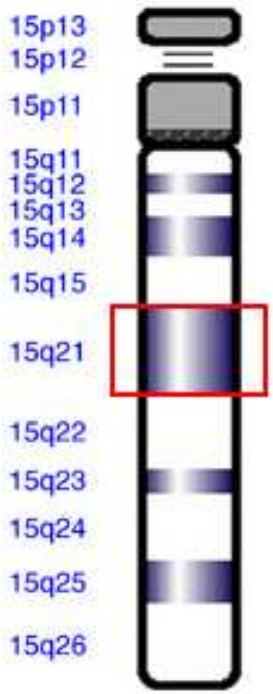
Einer der am häufigsten untersuchten Polymorphismen im ESR1 Gen ist der sogenannte PvuII Polymorphismus. Obwohl diese Genvariante im nicht kodierenden Teil des Rezeptorgens liegt, scheint sie auf die Stärke der Transkription des Gens einen Einfluss zu nehmen.

Auf Grund klinischer Untersuchungen konnte gezeigt werden, dass der p/p Genotyp die Östrogenwirkung am schwächsten vermittelt.
Deshalb geht man davon aus, dass dieser Polymorphismus entweder in die Transkriptionsgeschwindigkeit eingreift oder mit einer anderen funktionellen Genvariante assoziiert ist.



SYMBOL	rs NCBI	POLYMORPHISMUS
CYP17A1	**rs743572**	**T/C Pos. -34**

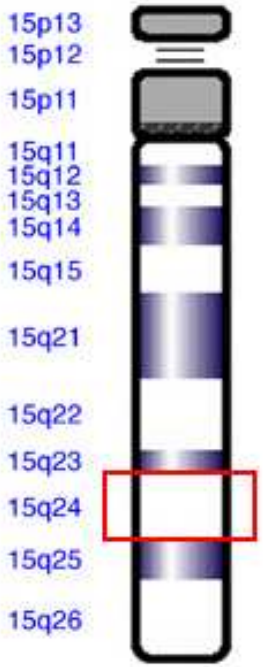
Dieser Polymorphismus wird auch als MspA1 A1/A2 bezeichnet. Der CYP17A1 -34 T/C Polymorphismus befindet sich in der Promoterregion des Gens.
Obwohl die Funktion dieses Basenaustausches noch nicht vollständig geklärt ist, konnte gezeigt werden, dass das C Allel mit einer erhöhten Transkription des Gens und bei Frauen mit erhöhten Serum Estradiol Spiegeln assoziiert ist.



SYMBOL	rs NCBI	POLYMORPHISMUS
CYP19A1	**rs 10046**	**C/T Pos. +1558**

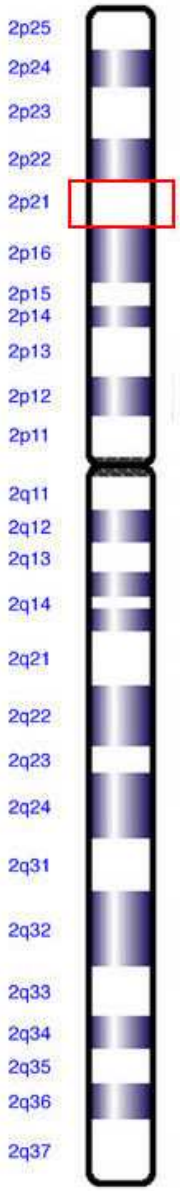
Einer der wohl am häufigsten untersuchten Polymorphismen im CYP19A1-Gen ist die C/T Pos. +1558 Variante in der so genannten „3‘ nicht translatierten Region“ des Gens. Eine funktionelle Rolle konnte diesem Polymorphismus bisher nicht zugeordnet werden, vielmehr geht man davon aus, dass C/T Pos. +1558 mit einem funktionellen Polymorphismus, der bis dato noch nicht identifiziert werden konnte, genetisch verbunden ist („linkage“).

Ungeachtet dessen geht dieser Basenaustausch bei postmenopausalen Frauen mit erhöhten Estrone und Estradiolspiegeln und einem erhöhten Verhältnis Estron : Androstenedion und Estradiol : Testosteron einher.



SYMBOL	rs NCBI	POLYMORPHISMUS
CYP1A1	**rs4646903**	**3801T>C (MspI)**
CYP1A1	**rs1048943**	**Ile462Val**

Der MspI und der Ile(462)Val SNP sind mit erhöhter Aktivität und Induzierbarkeit verbunden.



SYMBOL	rs NCBI	POLYMORPHISMUS
CYP1B1	**rs1056836**	**Leu432Val**
CYP1B1	**rs1800440**	**Asn453Ser**

Vor allem zwei Polymorphismen im CYP1B1 Gen wurden häufig untersucht. Der CYP1B1*3 (Leu/Val Codon 432), der mit gesteigerter Aktivität des CYP1B1 Enzyms und der CYP1B1*4 (Asn/Ser Codon 453), der mit verminderter Aktivität einhergehen kann.

CYP 1 A 1 SNP

CYP 1 B 1 SNP

2 Hydroxyöstradiol

4 Hydroxyöstradiol

16 Hydroxyöstradiol

17β Östradiol

Östron

E2

Männer 14 - 60 pg/ml

Frauen

- Follikelphase 22 - 215 pg/ml
- Ovulationsphase 191 - 572 pg/ml
- Lutealphase 22 - 232 pg/ml
- Postmenopause - 25 pg/ml

E1

Schwangerschaft :

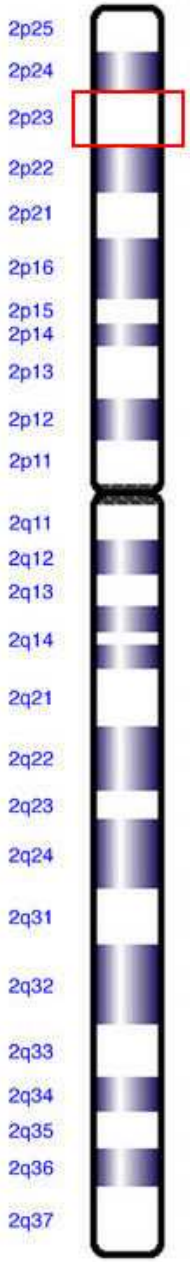
- 1.Trimester 61 - 715 pg/ml
- 2.Trimester 167 - 1860 pg/ml
- 3.Trimester 1040 - 3200 pg/ml

Postmenopause :

- mit Hormontherapie 40 - 346 pg/ml
- ohne Hormontherapie 14 - 102 pg/ml

Zyklus :

- Follikelphase 37 - 138 pg/ml
- Ovulationsphase 60 - 230 pg/ml
- Lutealphase 50 - 114 pg/ml



SYMBOL	rs NCBI	POLYMORPHISMUS
SRD5A2	**rs9282858**	**Ala49Thr**
SRD5A2	**rs523349**	**Val89Leu**

Vor allem zwei Polymorphismen, gehen mit einer Änderung der Steroid 5-alpha-reductase type 2 (SRD5a2) Aktivität einher, nämlich der Val89Leu und der Ala49Thr.

Der Val89Leu Austausch ist mit einer Reduktion der Aktivität verbunden, wohingegen der Ala49Thr Austausch in vitro mit einer 5 fach erhöhten Aktivität assoziiert ist.

5α Reduktase SNP

Testosteron

Dihydrotestosteron

Progesteron

5α -Progesteron

3α -Progesteron

T

Männer:
- 17 - 50 Jahre 2.8 - 8.0 ng/ml
- 50 - 82 Jahre 1.9 - 7.2 ng/ml

Frauen:
- 17 - 50 Jahre 0.07 - 0.73 ng/ml
- Postmenopause 0.04 - 0.69 ng/ml

DHT

Männer: 0.25 - 0.99 ng/ml

Frauen:
- Prämenopause 0.02 - 0.37 ng/ml
- Postmenopause - 0.18 ng/ml

PROG

Männer: 0,2 - 1,4 ng/ml

Frauen :
- Follikelphase 0.2 - 1.5 ng/ml
- Ovulationsphase 0.8 - 3.0 ng/ml
- Lutealphase 1.7 - 27 ng/ml
- Postmenopause 0.1 - 0.8 ng/ml

Schwangerschaft
- 1.Trimenon 13.0 - 44.0 ng/ml
- 2.Trimenon 44.0 - 175 ng/ml

KILM
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16.08.2010

RUNDSCHREIBEN

AN ALLE STATIONEN, AMBULANZEN UND EXTERNE EINSENDER

Löbliche Einsender!

Wir freuen uns, Ihnen ab sofort die Analyse genetischer Varianten im CYP2C19 Gen anbieten zu können.

[CANCER RESEARCH 58, 3307–3311, August 1, 1998]

A Prospective Study of *N*-Acetyltransferase Genotype, Red Meat Intake, and Risk of Colorectal Cancer[1]

Jia Chen,[2] Meir J. Stampfer, Heather L. Hough, Montserrat Garcia-Closas, Walter C. Willett, Charles H. Hennekens, Karl T. Kelsey, and David J. Hunter

Departments of Epidemiology [J. C., M. J. S., M. G-C., W. C. W., C. H. H., D. J. H.], Nutrition [M. J. S., W. C. W.], and Cancer Cell Biology and Environmental Health [K. T. K.], Harvard School of Public Health, the Harvard Center for Cancer Prevention [M. J. S., W. C. W., K. T. K., D. J. H.], Division of Preventive Medicine [C. H. H.], and Channing Laboratory, Brigham and Women's Hospital [J. C., M. J. S., H. L. H., M. G-C., W. C. W., K. T. K., D. J. H.], Harvard Medical School, Boston, Massachusetts 02115

ABSTRACT

Carcinogenic heterocyclic amines are activated by *N*-acetyltransferase (NAT) enzymes, encoded by *NAT1* and *NAT2*, to genotoxic compounds that can form DNA adducts in the colon epithelium. We have examined the relation of polymorphisms in the genes coding for both enzymes to risk of colorectal cancer and the gene-environment interaction with red meat intake among participants in the prospective Physicians' Health Study.

the less active N-hydroxyarylamide; this conversion is, thus, viewed as a detoxification reaction.

NAT2 is polymorphic, and the presence of multiple variant alleles divides the population into slow and rapid acetylators and may, thereby, influence individual susceptibility to genotoxic damage due to exposure to heterocyclic amines in cooked meat (9). A higher prevalence of rapid acetylators has been observed among colorectal

Heterocyclic amines are ini ially A'-oxidized by the polymorphic hepatic CYP1A23 enzyme and may then be O-acetylated by NATI (encoded by NAT!) or NAT2 (encoded by NAT2) to activated forms that can bind to DNA in thecolon epithelium

We observed a stronger association of red meat intake with cancer risk among *NAT rapid acetylators, especially among men 60 years old or older.*
Among those men who were rapid acetylators for both NATI and NAT2, consumption of > 1 serving of red meat per day was associated with a relative risk of 5.82 (95% CI, 1.11-30.6) compared with consumption of Â£0.5serving per day (P, trend = 0.02). These prospective data, which need to be confirmed in other studies, suggest that polymorphisms in the VU genes confer differential susceptibility to the effect of red meat consumption on colorectal cancer risk.

Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene

Avshalom Caspi,[1,2] Karen Sugden,[1] Terrie E. Moffitt,[1,2]*
Alan Taylor,[1] Ian W. Craig,[1] HonaLee Harrington,[2]
Joseph McClay,[1] Jonathan Mill,[1] Judy Martin,[3]
Antony Braithwaite,[4] Richie Poulton[3]

In a prospective-longitudinal study of a representative birth cohort, we tested why stressful experiences lead to depression in some people but not in others. A functional polymorphism in the promoter region of the serotonin transporter (5-HTT) gene was found to moderate the influence of stressful life events on depression. Individuals with one or two copies of the short allele of the 5-HTT promoter polymorphism exhibited more depressive symptoms, diagnosable depression, and suicidality in relation to stressful life events than individuals homozygous for the long allele. This epidemiological study thus provides evidence of a gene-by-environment interaction, in which an individual's response to environmental insults is moderated by his or her genetic makeup.

As genetic testing races ahead, doctors are left behind

Melissa Healy

Los Angeles Times | ARTICLE COLLECTIONS

October 24, 2009

An epidemic of risk factors for cardiovascular disease

What can be drawn from these observations? First, the potential costs in terms of mortality and health-care expenditure are massive. Cardiovascular disease is the major cause of death worldwide and accounts for 17% of health spending in the USA.