R E G I S T E R N O W !

1,000,000,000 *CHF investment*

7,000,874 *hours of work*

6,587 *experiments*

423 *researchers*

1 *medicine*

Health Hackathon 4.12 & 11.12.2025

THE MAKING OF AN INNOVATIVE MEDICINE

Introductory workshops on translational biomedical research, drug discovery and development

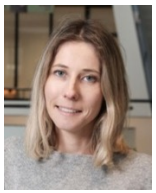
Judge Prof Dr med Olaia Naveiras

BIO-698 resumes Thursday September 11. 2025
4:15 PM @ CM013

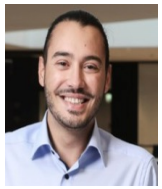
With Timothee Ferrari MD PhD cand

EPFL

Sciences de la Vie -SV



With Justine Epiney MD PhD cand



Mehdi AliGadiri MD PhD cand

Prof Roger G. Clerc

The Making Of An Innovative Medicine – class schedule

Thursday's @ 4-6 PM except 04.12/11.12.25 @2-6 PM

Session 1: **Scope of the course _ general organization _ case study**
11.09.25 *Embracing a career at the heart of biomedical research !?*
CM013

Session 2: **Historical perspective: the modern pharmacy**
18.09.25 *Advent of modern medicines - placebo controlled drug development*
CM013

Session 3: **Introduction to translational research: crossing the bridge**
25.09.25 *A chasm has opened wide between biomedical research and patients in need*
CM013

Sessions 4-5: **Therapeutic target identification I & II**
02-09.10.25 *"me too" vs a wealth of innovative targets _ small MW cpds vs biologicals*
CM013 *Early front loading of biomarker identification for cohort stratification*

Session 6: **Structure based drug design _medicinal chemistry_low/high throughtput**
16.10.25 **screening assays_ multiple parallel optimization_ML-powered screens**
CM013 *Setting up screening assays, the robotics, the million cpds librairies*

Session 7: **Therapeutic modalities biologicals–peptides : today's - tomorrow's**
30.10.25 **pharmacy NBEs**
CM013 *Challengies (cost of goods - healthcare payers) and opportunities*

The Making Of An Innovative Medicine - class schedule

Thursday's @ 4-6 PM except 04.12/11.12.25 @2-6 PM

Session 8: **Personalized Healthcare PHC _ precision medicine**
06.11.25 *How PHC started: from a single case to a paradigm change*
CM013

Session 9: **Pharmacogenetic polymorphisms, Pharmacogenomics**
13.11.25 *Interindividual variability toxicity in response to medicines*
CM013

Session 10: **In vivo pharmacology, investigative toxicology with Nathalie Brandenberg PhD eMBA CEO**
20.11.25 *Preclinical research ends up with IDB's, FDA guidelines for FIH*
CM013

Session 11: **Clinical research_ phase 0, phase I, II, III, IV with Raphael Sommer PhD Bristol Myers Squibb**
27.11.25 *The long and complex experimental procedures with human patients*
CM013

Intellectual property_ integrity in research_my genome vs our genomes
Why are patents essential to new medicine/biotech development

Session 12: **Health Hackathon – Hacking medicine I with T. Ferrari & M. Ali Gadiri MD PhDs confirmed !**
04.12.25 *Pitches –building teams – hacking problem - 5Ws – brainstorm*
starts @ 2PM ! CO017

Session 13: **Health Hackathon – Hacking medicine II with judges Prof Olaia Naveiras - Prof James Habib**
11.12.25 *Building up solutions – make it better - final presentations*
starts @ 2PM ! CO017

WORKSHOP LISTING - THE MAKING OF AN INNOVATIVE MEDICINE BIO 698-HS2025 in CM013			
! NON EXHAUSTIVE LISTING - SUGGESTIONS WELCOME !			
sessions		workshops	speaker/s
S02 (18-09-25)			
historical medicines		penicilin: impact, whose invention ?	
hopping on giant shoulders		prozac at the core of psychiatry	
		vaccine discovery:smallpoxJennerTodaymRNAvaccin	Eugenio
		artemisinin and malaria	
		insulin-Banting Best et al. beagle dog	
		slide51-X-ray image DNA--Rosalind Franklin	
		cyclosporin from soil sample to life saver	
S03 (25-09-25)			
translational research		expanding scope of translational therapies	
from bench to bedside and back		chronotherapy,circadian clock,sex,longevity	Solomon
		CAR-T, TCR-T cell therapies in "cold" tumors	
		Y chrom loss in immune cells drives cancer	
S04 (02-10-25)			
therapeutic target identification		th. target identification using a phenocopy screen	Justine
S05 (09-10-25)		nocosomial inf/MRSA/phage antibacterials	
therapeutic target identification		Crispr/Cas9 gene editing huntington disease	
		AI in drug discovery / ML-powered medicine	Lou
		AIDS - Lenacapavir : end of plague ?	
S06 (16-10-25)			
structure based drug design		macrocycles and non druggable targets	Benedikt
		chemoproteomics - NMEs	
		AIDS HIV from deadly virus to chronic disease	
S07 (30-10-25)			
therapeutic modalities - NBEs		rare diseases repurposing medicines	Jana
		biologics on the rise-MABs medicines & more	Eleni
		RNA therapeutics, antisense medicines	
		Wnt pathway - PROTACs vs molecular GLUEs	
S08 (06-11-25)			
PHC personalized healthcare		BRCA1/2 preventive surgery/tumor board	
Human genomics		4P medicine-GWAS-**P**ersonalized **H**ealth **C**are	Frederico
		disease enabling biomarkers/micro RNAs	
		AZ-biomarker BD-tau yet still no curative drug	
		centenarian host isoallo-LCA bile acid bacteria	
S09 (13-11-25)			
pharmacogenetic polymorphism		Pharmacogenomics	Greta
		deCODE Inc pharmgenomic/iceland genealogy	
		ageing and thanatophobia	
S10 (20-11-25)			
in vivo pharmacology		guest speaker : profiling MABs on organoids	Nathalie B
toxicology		organoids-drug discovery - CF patients	Tianhao + Alice
		thalidomide repurposing mulitple myeloma	
S11 (27-11-25)			

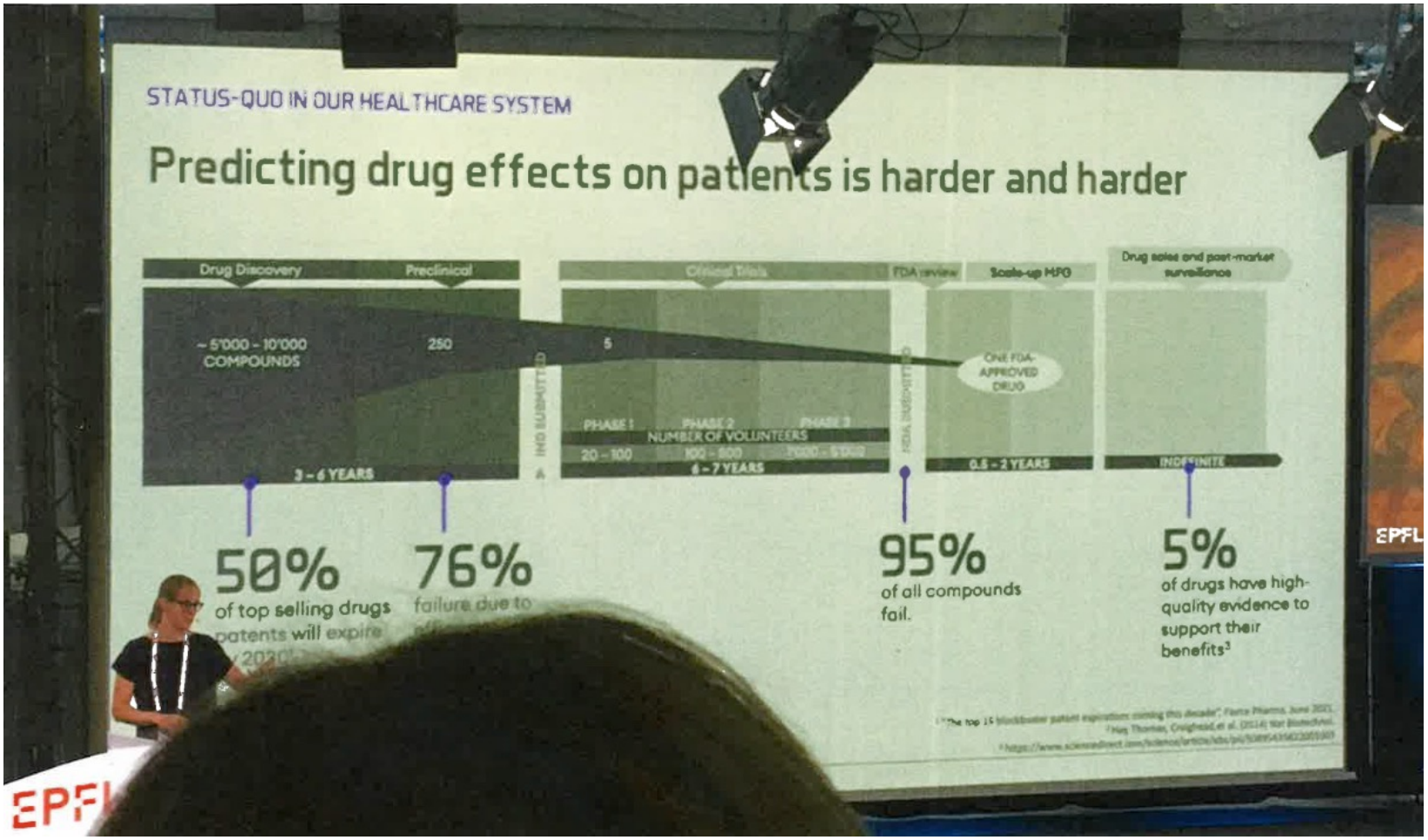
Workshops
The Making Of An Innovative Medicine
(today's class)

Prof O Naveiras

Prof J Habib

BIO 698 - session 10 : Dr N Brandenberg on colorectal cancer
EPFL CM013 Thursday November 20. 2025 4 PM

Guests welcome !



Host : honorary professor and lecturer Roger G Clerc

MyHeritage

Session 9

- Pharmacogenetic polymorphisms _ Pharmacogenomics_GWAS

Headquarters: Founded: Shenzhen, China

Complete GENOMICS
Powered by MGI

Headquarters: Pleasanton, U.S.

10X GENOMICS

Headquarters: California

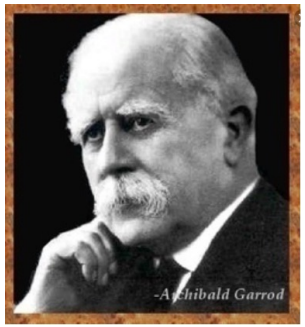
ULTIMA GENOMICS

BGI

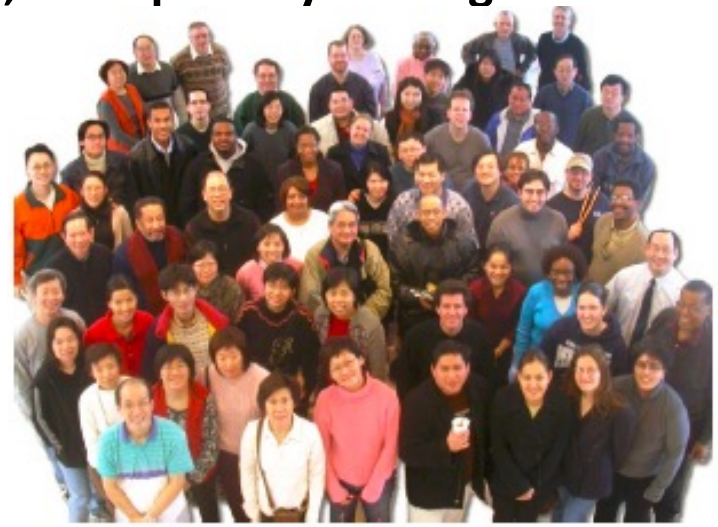
BGI headquarters in Shenzhen

PHC _ Pharmacogenomics, pharmacogenetics

PHARMACOGENETICS, PHARMACOGENOMICS : the study of genetically based interindividual variability in response to drugs; susceptibility to drug induced adverse effect



Pharmacogenetics is not new !
1902 A. Garrod MD suggested that genetic factors direct chemical transformation in humans and underlie individual variability
1959 F. Vogel coined the term "pharmacogenetics"



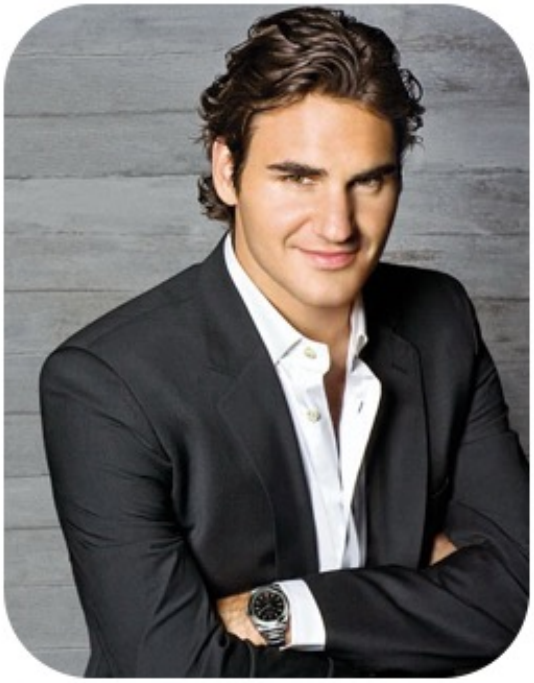
cohort

Patients are individuals, we all are different ! (except twins)

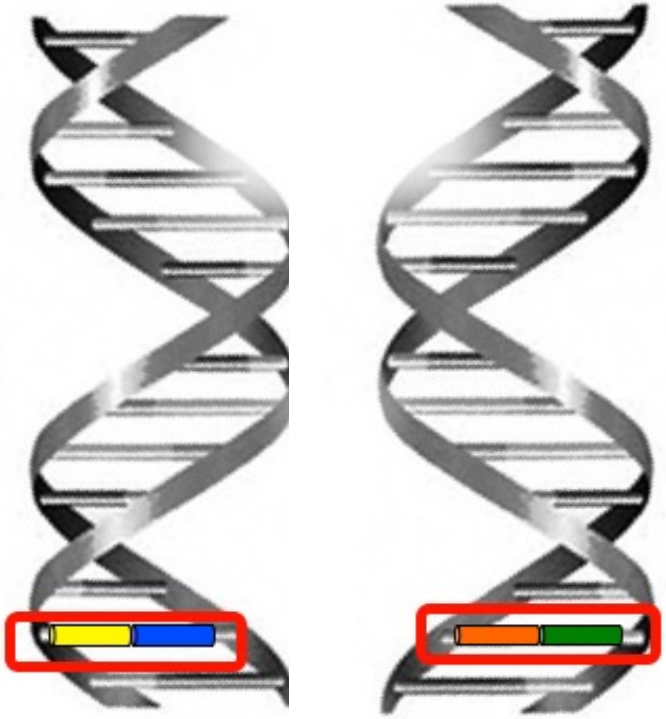
PHARMACOGENOMICS : A DIRECT LINK TO PERSONALIZED HEALTHCARE PHC !

WHY DOES SOMEONE NEED TWICE A STANDART DOSE OF A MEDICINE FOR AN EFFICACIOUS TREATMENT WHEREAS ANOTHER PATIENT MAY EXPERIENCE SERIOUS ADVERSE EFFECTS UNDER THE SAME POSOLOGY ?

Human Genome revolution : Single Nucleotide Polymorphisms_ SNPs



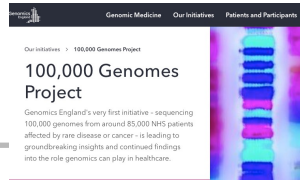
Roger Federer



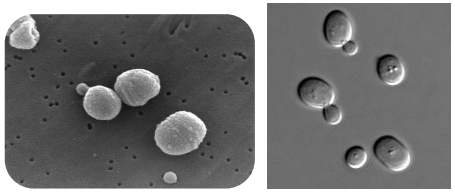
Lauriane Sallin

- Personalized genomics : we **human beings are 98.% identical** yet… ~1.8% different out of ~3x10<9 nucleotides
- **~3x10<6 SNP's (single nucleotide polymorphisms) different between individuals** located about every thousands base pair except for… genetically identical twins !

The genome sequence revolution: breakthroughs and risks from life science discoveries



One of the first mammalian/human genome fully sequenced (2000)



S. Pneumoniae S. cerevisiae one of the first genomes fully sequenced (1995)

Today (2025) millions of human genomes fully sequenced !

finances

health plan may no longer consider you ! ¨ or else at high cost based on your predisposition polymorphism ?

ethics

scientific progress = novel discoveries

vie privée: qui a le droit de savoir? psychologie: conséquences du diagnostic? où sont les limites ? discrimination: races, IQ, sexe ?

business politics

medical advances

class action

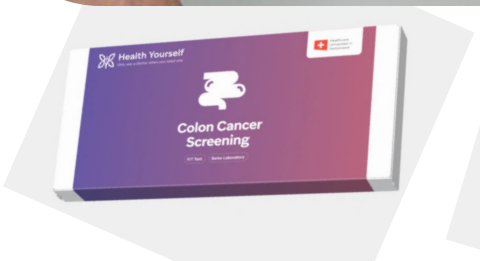
privacy: caught in justice because of your ancestors ?

WORKSHOP !

Genetic business, forensic, my DNA everywhere !

Internet website xyz →

my saliva sent off !
DNA mouth swab



↓

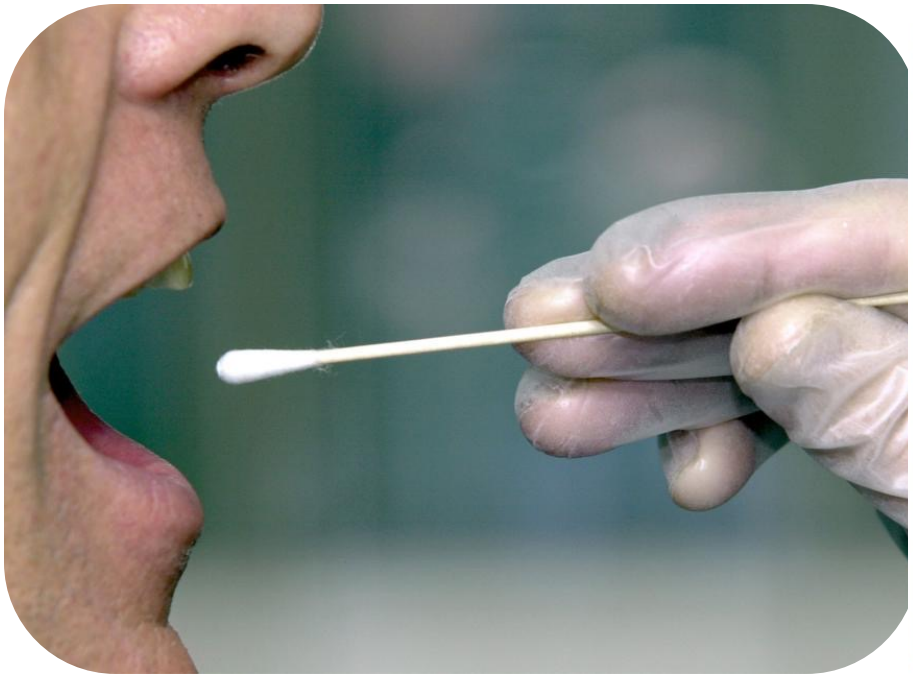
Personal identification

- COMPARAISON DE DEUX GÉNOMES
- CARACTÉRISTIQUES PERSONNELLES
- ORIGINES ET CONNAISSANCES DES ANCETRES
- POURCENTAGE DE CHANCE DE CONTRACTION D'UNE MALADIE !?

Genetic big business, forensic, my DNA everywhere !

curious about their genealogy, many customers ignore the potential trade off

Internet website xyz → **a DNA mouth swab…easy where did I sent off my mouth epithelial cells ?!**



Unternehmen machen mit der Neugier auf das Erbgut Geld – nicht immer sind sich die Kundinnen und Kunden darüber im Klaren.

Any solution to the confrontation between life science research and ethics ?

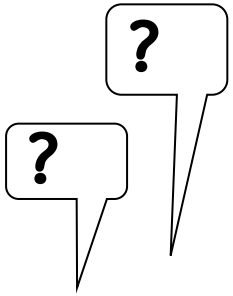
- engage with an open dialogue between biomedical scientists and the population at large !

compelling dialogue

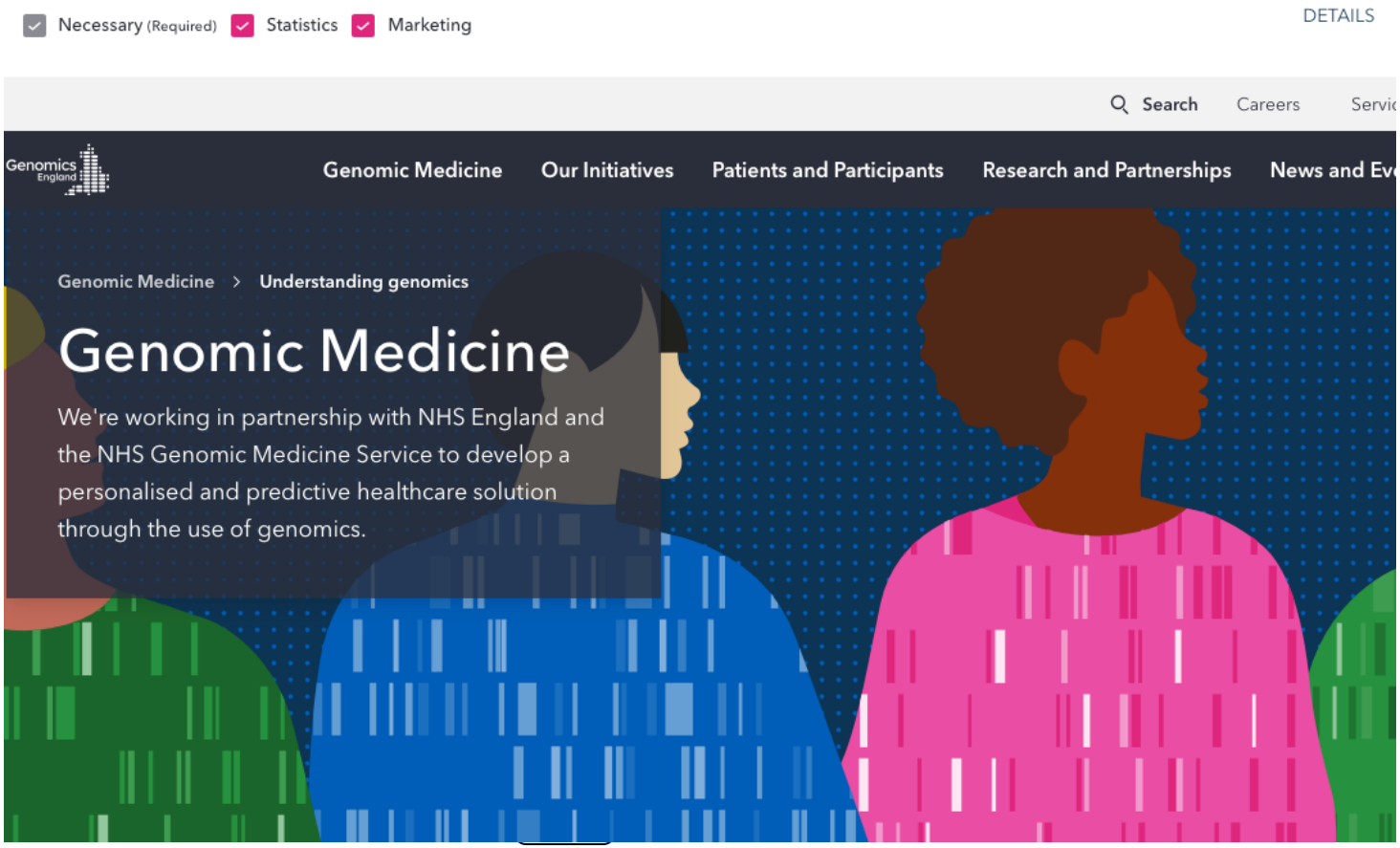
Academia ! Pharma ! Start up !

Any solution to the confrontation between life science research and ethics ?

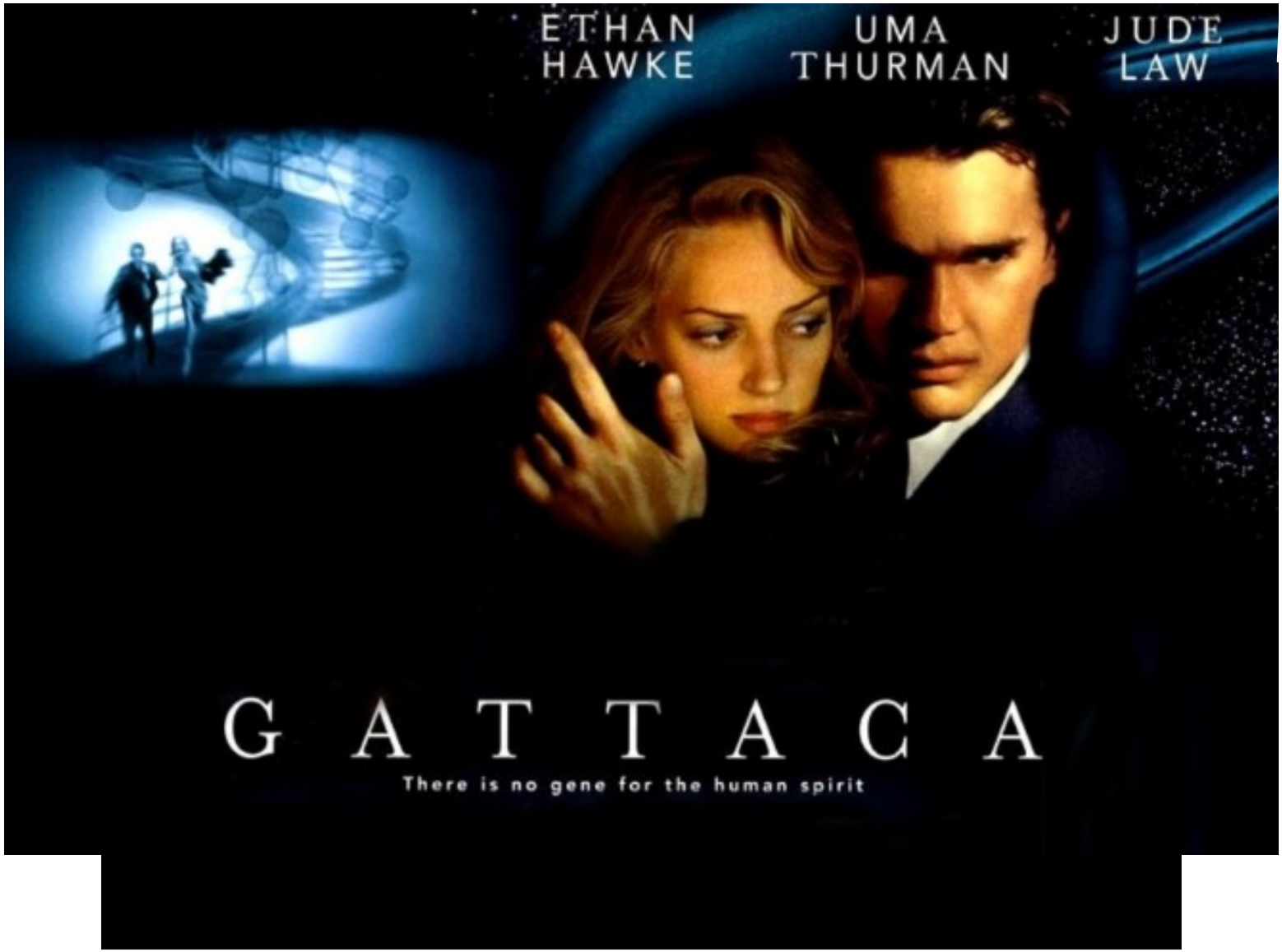
- engage with an open dialogue between biomedical scientists and the population at large !



compelling dialogue eg NHS England

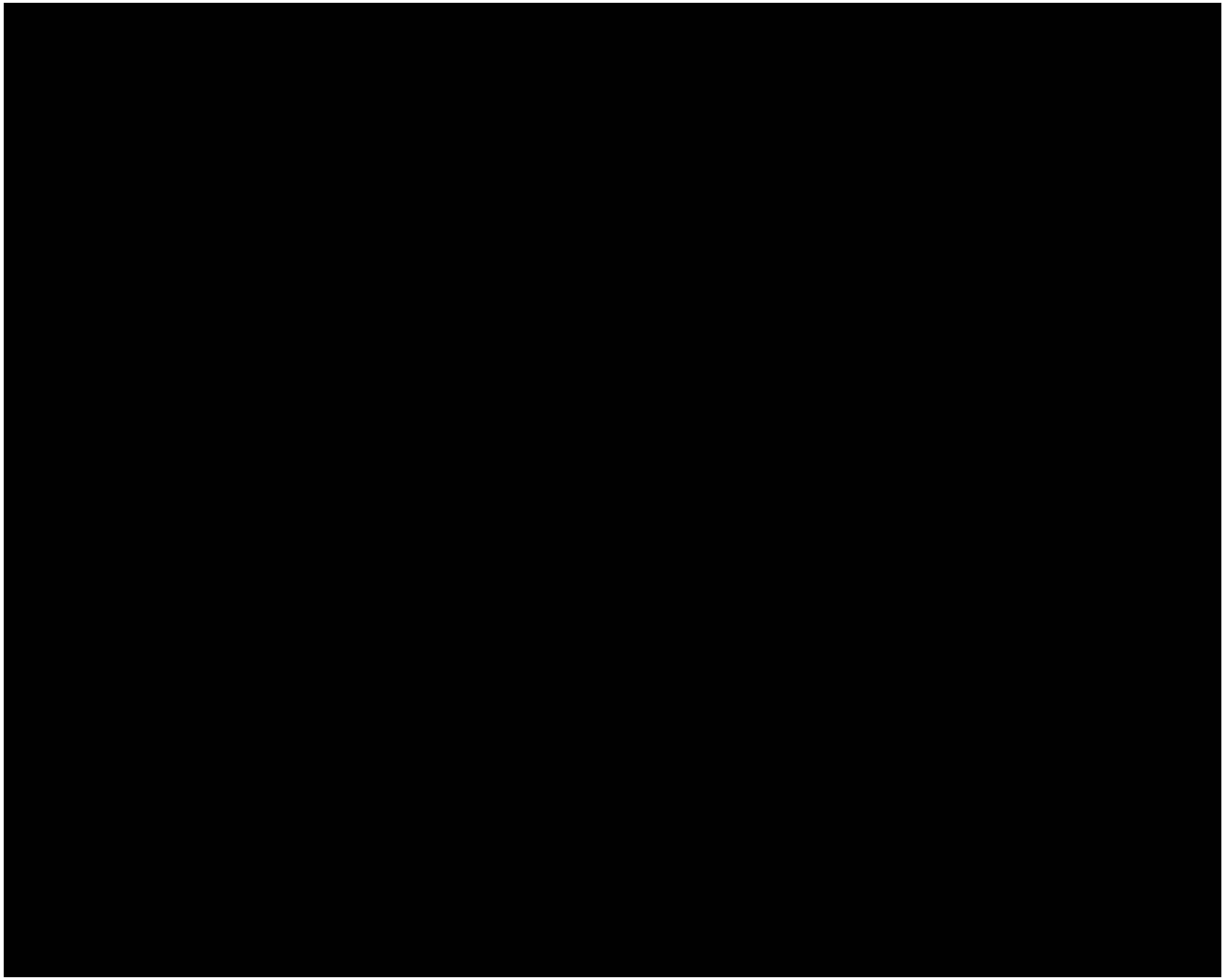


Welcome to GATTACA science fiction – the genotype of my kids at will ?



Welcome to GATTACA – today science fiction, tomorrow reality ?

Welcome to GATTACA – the genotype of my kids at will ?



Welcome to GATTACA – the genotype of my kids at will ?
"ONE GENE ONE PROTEIN" BIOLOGICAL FACT OUTDATED ?

TODAY OUR BLUEPRINT ENABLES TO THRAWT FEW KNOWN SINGLE GENE INHERITED DISEASES , eg T21, PKU.

TOMORROW A DROP OF BLOOD MAY ENABLE ….

- CHOOSING THE SEXE, THE HAIR, EYE COLOUR AND MORE OF OUR OFFSRPING

- DEFINE THEIR PROFESSIONAL FUTURE, THE IQ ?

WILL EPIGENETICS CHANGE OUR PERCEPTION /EXPECTATION OF MEDICAL GENETICS ?

GATACA NO LONGER PROFILES A « CLASSICAL » EPIGENETICS (eg. testicular, fallopian tube ablation) BUT RATHER INVITES A SUBLTE SOPHISTICATED AND ATTRACTED TO SMART PEOPLE OPPORTUNITY TO GENERATING HUMAN KINDS AT THEIR WILL – A KIND OF EUGENICS 2.0 - A SCARESOME GATTACA PERSPECTIVE

CRISPR twin girls : human germline gene editing reported :
many fears of “designer babies” and widespread concerns for the impact of this technology on human evolution and its implications in social Darwinism

A Chinese scientist claims that twin girls have been born whose genomes were edited at the embryo stage.

GENOMICS

International outcry over geno

The revelation f … liting.

BY DAVID CYRANOSKI &

Scientists are shocl… has been lim-
reports that a Chi… ate the benefit
to have helped m… inate disease-
genome-edited babies – …an germ line.
born this month. …ed off-target
He Jiankui, a genom… concerns.
at the Southern Unive… na's clinical-
Technology of China i… d the popular
he impregnated a wom… tool to disable
had been edited to disab… odes a protein
HIV uses to infect cells. …ell. Genome-
…ov was asked
leap in the use of genome editing. Until now, … to review documents that described the ▶

experiment immediately generated massive concern over the moral impact of this human experiment and earned universal condemnation for advancing to human experi- mentation without adequate safety precautions and assessments.

CRISPR babies : mostly European subjects with homologous CCR5-∂32/∂32 are highly resistant to HIV, while heterozygous carriers have reduced susceptibility

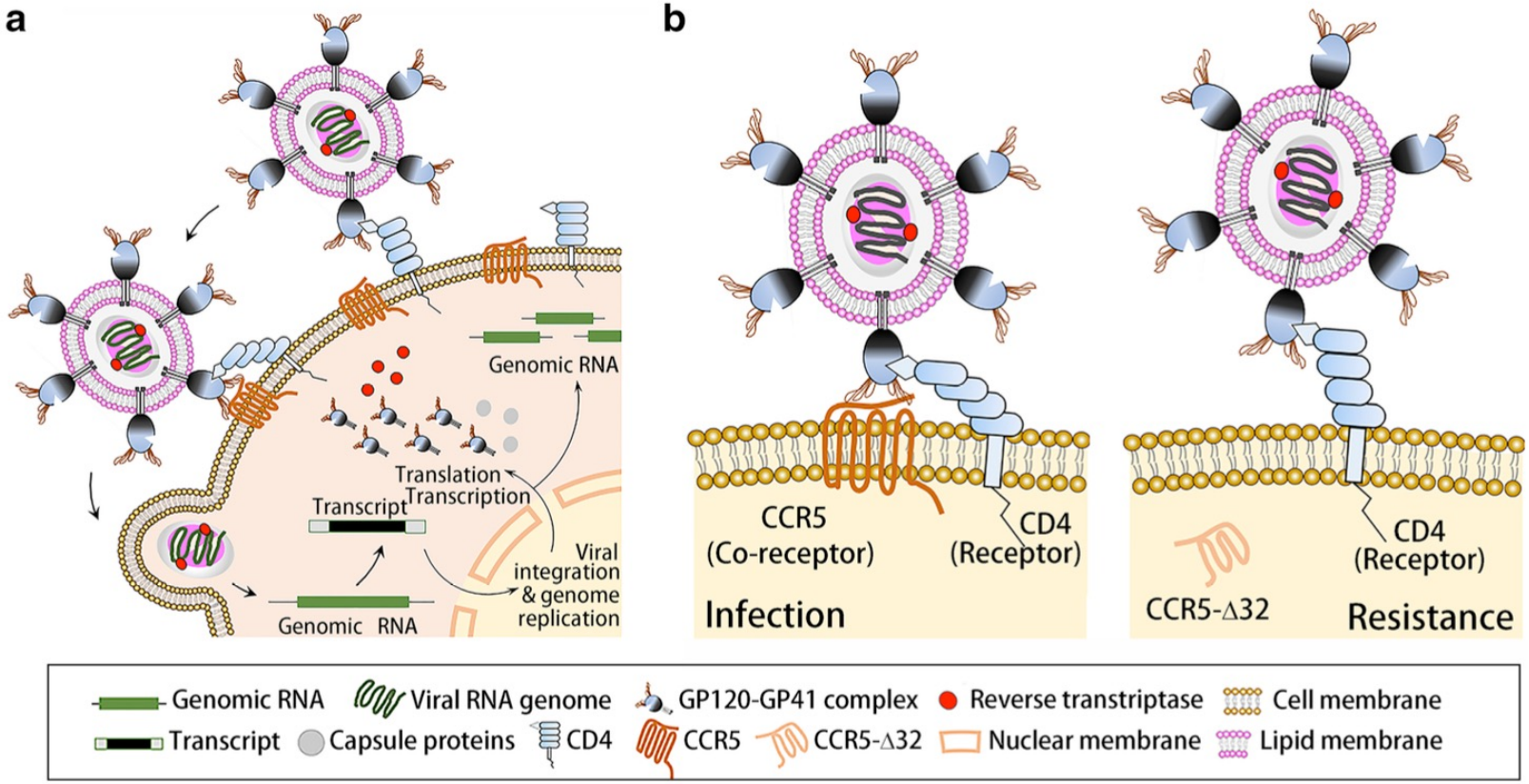
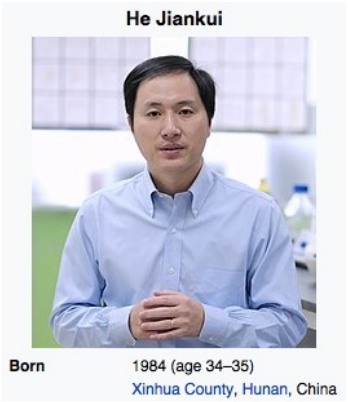
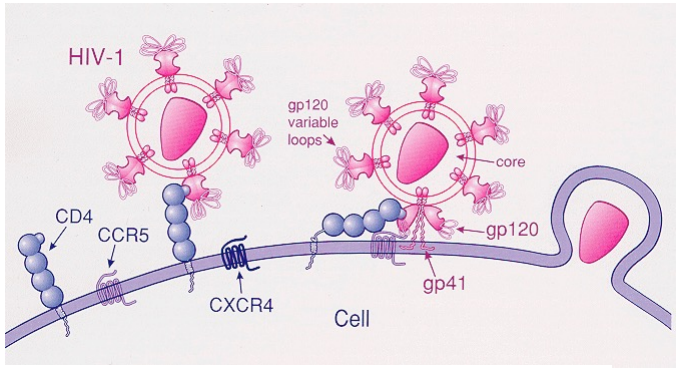


Fig. 1 The HIV infection process (**a**): The HIV GP-120 first associates with both the CD4 and CCR5 on the surface of a cell, which is the first step in viral invasion and further viral replication. Molecular mechanism of CCR5 in HIV infection and the protective effect of cytoplasmic CCR5-Δ32 against HIV-1 infection (**b**)

ON He Jiankui's CASE : « WE DO HAVE REASON TO BE CONCERNED: IF ANYONE WORKING IN THE FIELD GETS INDICATIONS THAT IT IS HAPPENING, IT IS IMPORTANT THEY LET AUTHORITIES KNOW » NL David Baltimore

CRISPR babies : December 30. 2019, He Jiankui (34) was sentenced 3 years jail, fined 3 millions Yuan (430,000 US $) and banned from performing any biomedical research





The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 MARCH 6, 2014 VOL. 370 NO. 10

Gene Editing of *CCR5* in Autologous CD4 T Cells of Persons Infected with HIV

Pablo Tebas, M.D., David Stein, M.D., Winson W. Tang, M.D., Ian Frank, M.D., Shelley Q. Wang, M.D., Gary Lee, Ph.D., S. Kaye Spratt, Ph.D., Richard T. Surosky, Ph.D., Martin A. Giedlin, Ph.D., Geoff Nichol, M.D., Michael C. Holmes, Ph.D., Philip D. Gregory, Ph.D., Dale G. Ando, M.D., Michael Kalos, Ph.D., Ronald G. Collman, M.D., Gwendolyn Binder-Scholl, Ph.D., Gabriela Plesa, M.D., Ph.D., Wei-Ting Hwang, Ph.D., Bruce L. Levine, Ph.D., and Carl H. June, M.D.

CRISPR twin girls do not carry the exact *CCR5-Δ32/Δ32* mutation hence He Jiankui carried out the false gene editing !

The New York Times

Scientists Seek Moratorium on Edits to Human Genome That Could Be Inherited

David Baltimore, former president of the California Institute of Technology, helped organize an international group of scientists to discuss use of the Crispr-Cas9 technique on human genes. Susan Walsh/Associated Press

HIV medical need : 2022 : **470** new cases in sex health clinics registered in Switzerland

DO YOU WANT EDITORIAL CHANGES (POSSIBLY DELETERIOUS, OFF TARGET) TO THE HUMAN GERMLINE BE INHERITED BY THE GIRL'S CHILDREN AND THUS CONTRIBUTE PERMANENT CHANGES TO THE HUMAN GENE POOL ?

ON He Jiankui's CASE : « WE DO HAVE REASON TO BE CONCERNED: IF ANYONE WORKING IN THE FIELD GETS INDICATIONS THAT IT IS HAPPENING, IT IS IMPORTANT THEY LET AUTHORITIES KNOW » NL David Baltimore

CRISPR human germline gene editing in New York 2025 ! : entrepreneur Cathy Tie's company *Manhattan Genomics* will work on methods to edit the genomes of human… NO WE DO NOT AGREE !

NEWS | 03 November 2025 | Correction 04 November 2025

‘Biotech Barbie’ says the time has come to consider CRISPR babies. Do scientists agree?

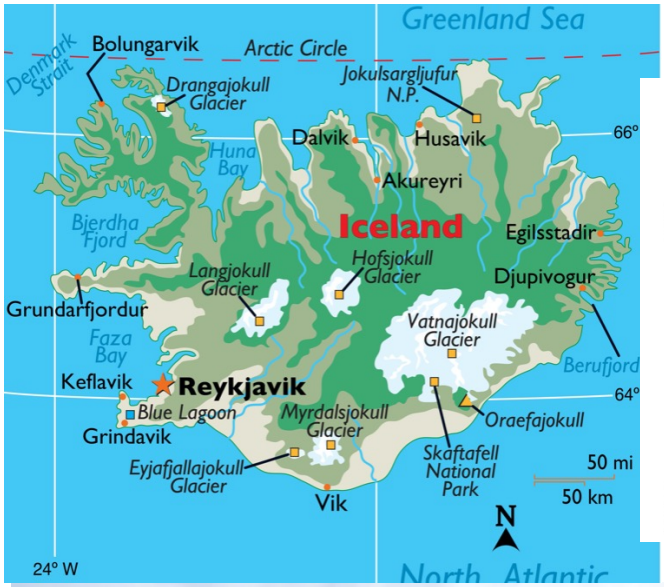
A company’s plan to edit the genomes of human embryos worries some researchers – but it might reflect the changing attitudes towards the controversial approach.

By Heidi Ledford

These experiments on human germ line experiment massive concern over the moral impact of such lab work and shall earn universal condemnation for advancing to human experimentation without adequate safety precautions and assessments.

Entrepreneur Cathy Tie’s company Manhattan Genomics will work on methods to edit the genomes of human embryos. Credit: Caitlyn Gaurano

Iceland_ obsessed with genealogy : remembering ancestors 10th generation back ?



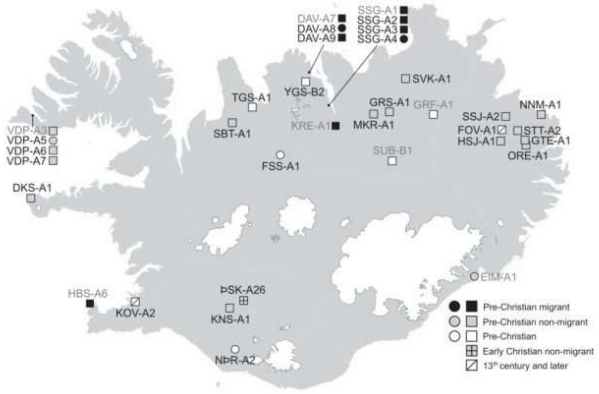


Fig. 1. A map of Iceland showing the locations of skeletal remains sampled for this study. Circles indicate females and squares, males. Eight samples (light gray labels) were ultimately excluded from further analysis.

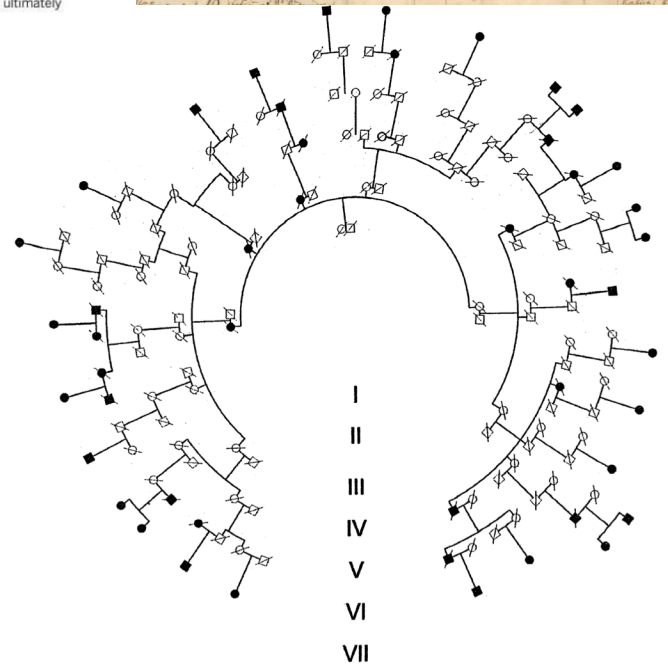


Figure 1 This is an example of a pedigree, which includes a large number of individuals living more than 90 years (filled circles and squares). The pedigree reaches six generations back to the year 1730. Not all siblings or relatives are shown, but the average number of siblings of the 27 long-lived individuals still living is about five.

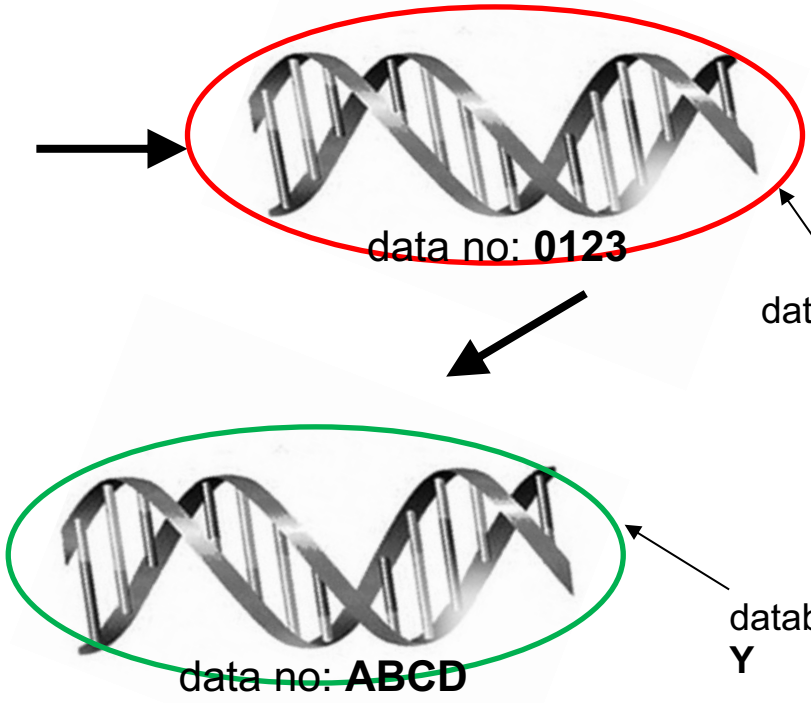
an Journal of Human Genetics

SNPs _ double encryptment of SNPs databases : deCODE genetics - pioneers in genome data protection

https://www.decode.com

securing Mr Sample proprietary data

Mr Sample's genomic sequence has been stored under code #0123, followed by a second code #ABCD



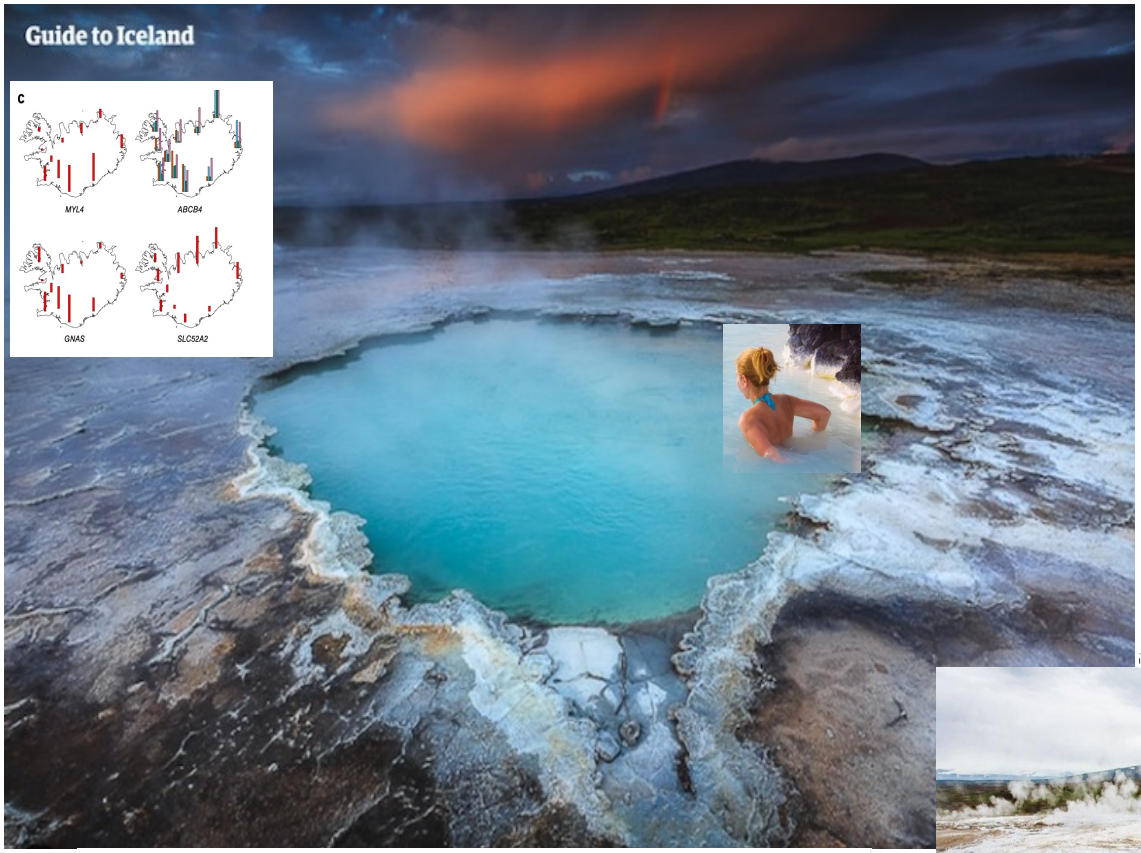
eg: deCODE genetics community partnership and the Icelandic Ministry of Health centralized database on healthcare

Government of Iceland
Ministry of Health

Protection of privacy

The database will be continuously monitored by the Data Protection Commission of Iceland. All personal identifiers will be encrypted in the institutions where the information is generated and again before the data arrive at the database. Users will access it

deCODE genetics : SNPs _ double encryptment of SNPs databases



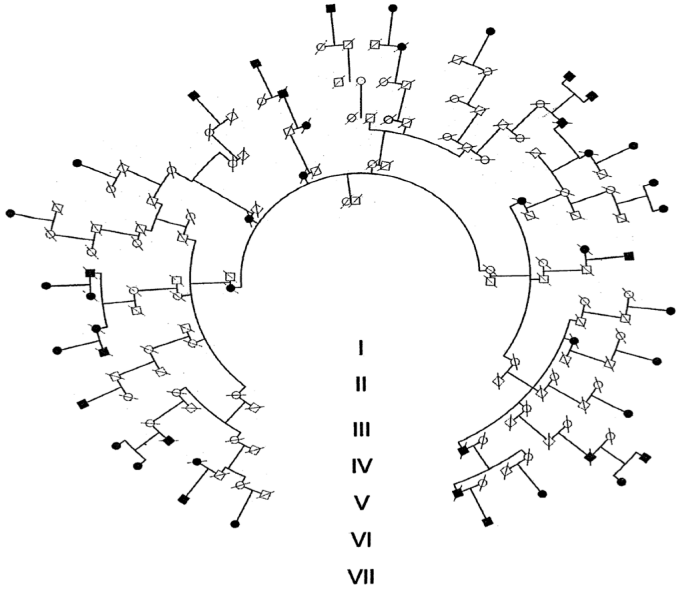
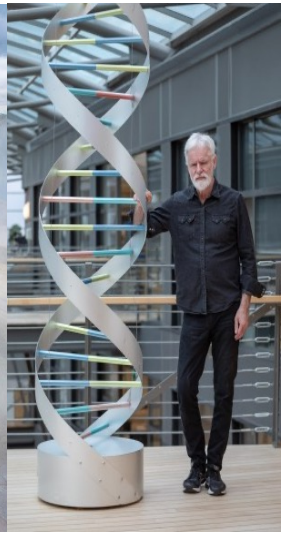


Figure 1 This is an example of a pedigree, which includes a large number of individuals living more than 90 years (filled circles and squares). The pedigree reaches six generations back to the year 1730. Not all siblings or relatives are shown, but the average number of siblings of the 27 long-lived individuals still living is about five.

ıropean Journal of Human Genetics

deCODE genetics

a subsidiary of AMGEN



deCODE genetics : whole genome sequencing : mutation rate

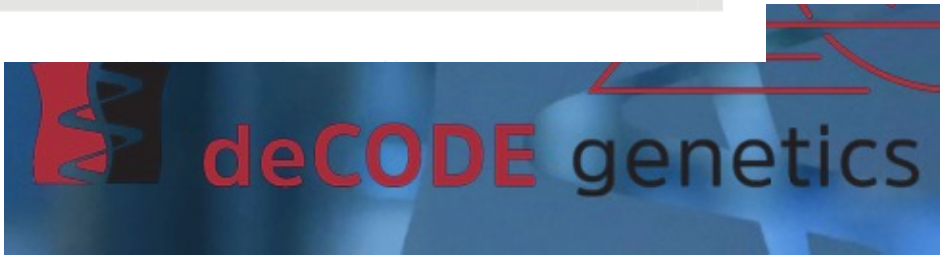
ARTICLE

doi:10.1038/nature11396

Rate of *de novo* mutations and the importance of father's age to disease risk

Augustine Kong[1], Michael L. Frigge[1], Gisli Masson[1], Soren Besenbacher[1,2], Patrick Sulem[1], Gisli Magnusson[1], Sigurjon A. Gudjonsson[1], Asgeir Sigurdsson[1], Aslaug Jonasdottir[1], Adalbjorg Jonasdottir[1], Wendy S. W. Wong[3], Gunnar Sigurdsson[1], G. Bragi Walters[1], Stacy Steinberg[1], Hannes Helgason[1], Gudmar Thorleifsson[1], Daniel F. Gudbjartsson[1], Agnar Helgason[1,4], Olafur Th. Magnusson[1], Unnur Thorsteinsdottir[1,5] & Kari Stefansson[1,5]

Mutations generate sequence diversity and provide a substrate for selection. The rate of *de novo* mutations is therefore of major importance to evolution. Here we conduct a study of genome-wide mutation rates by sequencing the entire genomes of 78 Icelandic parent–offspring trios at high coverage. We show that in our samples, with an average father's age of 29.7, the average *de novo* mutation rate is 1.20×10^{-8} per nucleotide per generation. Most notably, the diversity in mutation rate of single nucleotide polymorphisms is dominated by the age of the father at conception of the child. The effect is an increase of about two mutations per year. An exponential model estimates paternal mutations doubling every 16.5 years. After accounting for random Poisson variation, father's age is estimated to explain nearly all of the remaining variation in the *de novo* mutation counts. These observations shed light on the importance of the father's age on the risk of diseases such as schizophrenia and autism.



Kong et al. 2013 Nature 488:4 71-489

deCODE genetics: GWAS shows father's age matters

RESEARCH ARTICLE

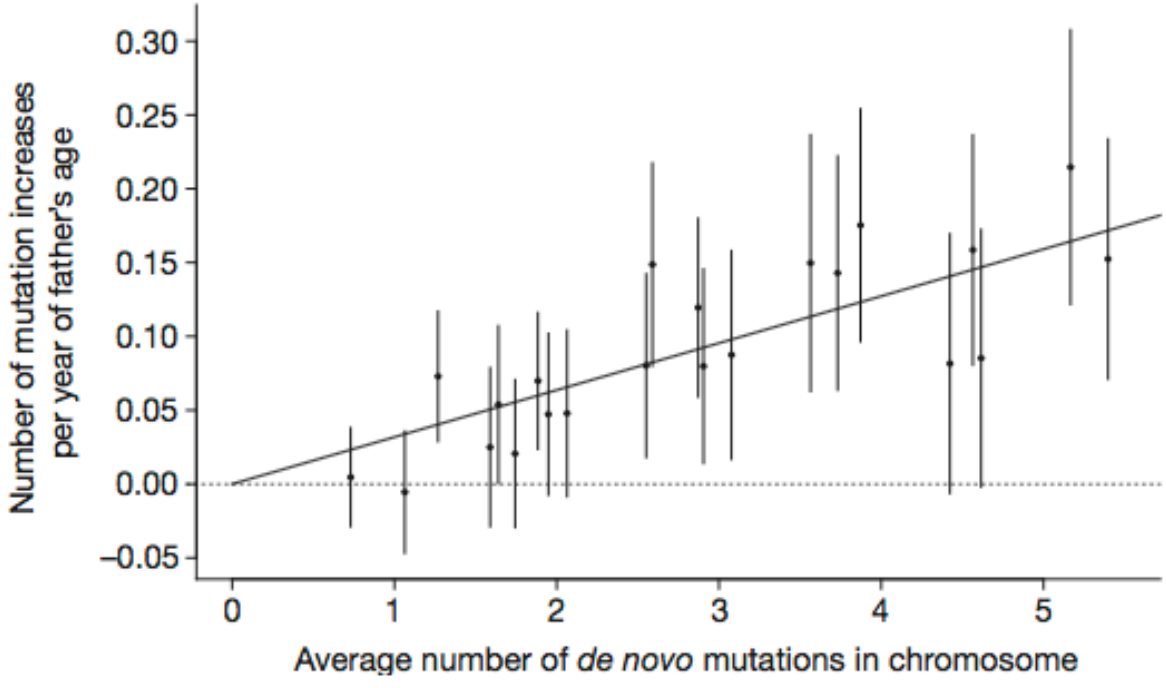
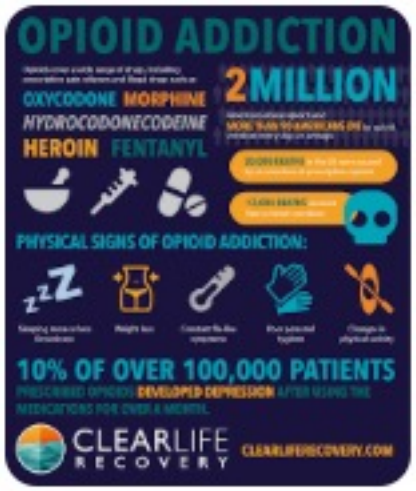


Figure 3 | Effect of father's age by chromosome. By chromosome, the

autism cases increasing : ageing parents ? improved diagnostics ? premature birth ?

Kong et al. 2013 Nature 488:4 71-489



deCODE genetics : GWAS on opioid addiction heritability

scientific reports

Check for updates

Multi-trait genome-wide association study of opioid addiction: *OPRM1* and beyond

Nathan Gaddis[1,28], Ravi Mathur[1,28], Jesse Marks[1], Linran Zhou[1], Bryan Quach[1], Alex Waldrop[1], Orna Levran[2], Arpana Agrawal[3], Matthew Randesi[2], Miriam Adelson[4], Paul W. Jeffries[3], Nicholas G. Martin[5], Louisa Degenhardt[6], Grant W. Montgomery[7], Leah Wetherill[8], Dongbing Lai[8], Kathleen Bucholz[3], Tatiana Foroud[8], Bernice Porjesz[9], Valgerdur Runarsdottir[10], Thorarinn Tyrfingsson[10], Gudmundur Einarsson[11], Daniel F. Gudbjartsson[11], Bradley Todd Webb[1], Richard C. Crist[12], Henry R. Kranzler[12], Richard Sherva[27], Hang Zhou[13], Gary Hulse[14], Dieter Wildenauer[14], Erin Kelty[15], John Attia[16], Elizabeth G. Holliday[16,17], Mark McEvoy[16,17], Rodney J. Scott[18], Sibylle G. Schwab[19], Brion S. Maher[20], Richard Gruza[21], Mary Jeanne Kreek[2,29], Elliot C. Nelson[3], Thorgeir Thorgeirsson[11], Kari Stefansson[11,22], Wade H. Berrettini[12], Joel Gelernter[23],

(b)

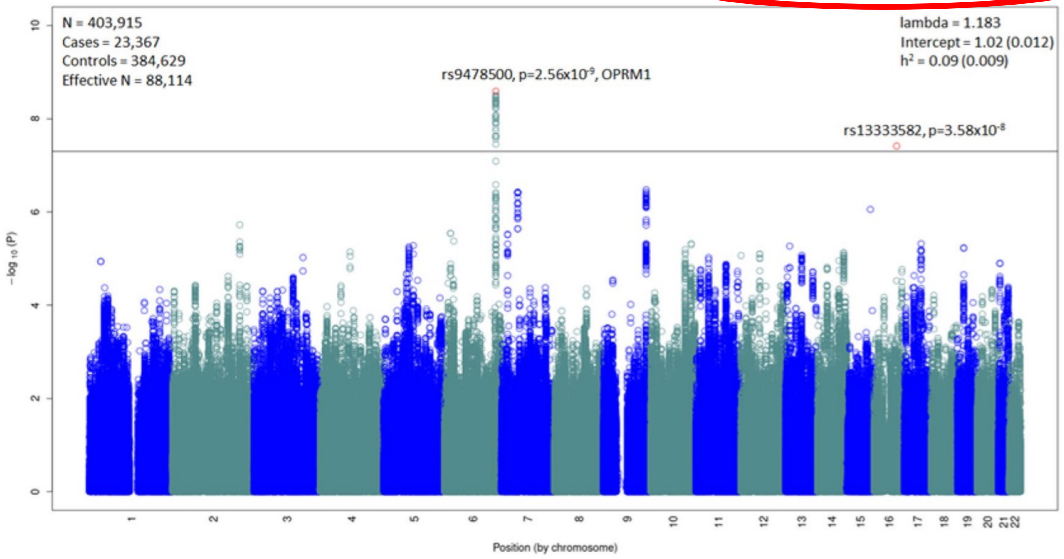


Figure 1. Genomic SEM model and Manhattan plot. (**a**) A common factor (p_g) gSEM model (using

deCODE genetics : behavioural studies on opioid addiction

www.nature.com/scientificreports

scientific reports

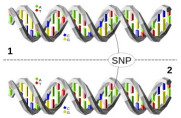
Check for updates

OPEN

Variation of the human mu-opioid receptor (OPRM1) gene predicts vulnerability to frustration

Alan M. Daniel, Brenda G. Rushing & Karla Y. Tapia Menchaca

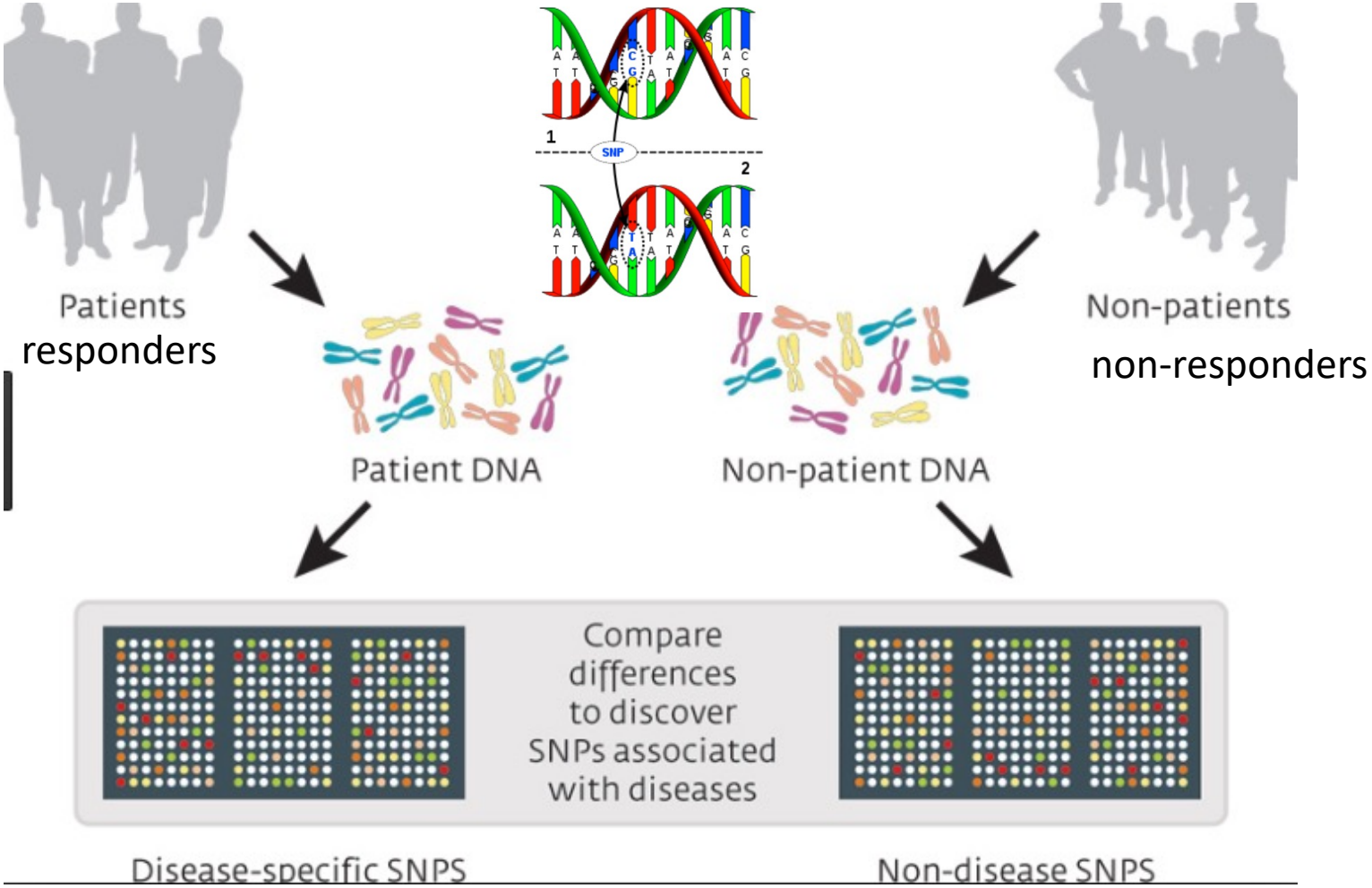
Understanding the emotional reaction to loss, or frustration, is a critical problem for the field of mental health. Animal models of loss have pointed to the opioid system as a nexus of frustration, physical pain, and substance abuse. However, few attempts have been made to connect the results of animal models of loss to human behavior. Allelic differences in the human mu opioid receptor gene, notably the A118G single nucleotide polymorphism, have been linked to individual differences in pain sensitivity, depressive symptoms, and reward processing. The present study explored the relationship between A118G and behavior in two frustrating tasks in humans. Results showed that carriers of the mutant G-allele were slower to recover behavior following a reward downshift and abandoned a frustrating task earlier than those without the mutation. Additionally, G-carriers were more sensitive to physical pain. These results highlight the overlap between frustration and pain, and suggest that genetic variation in opioid tone may contribute to individual differences in vulnerability and resilience following emotional disturbances.



GWAS– Impact on personalized healthcare PHC

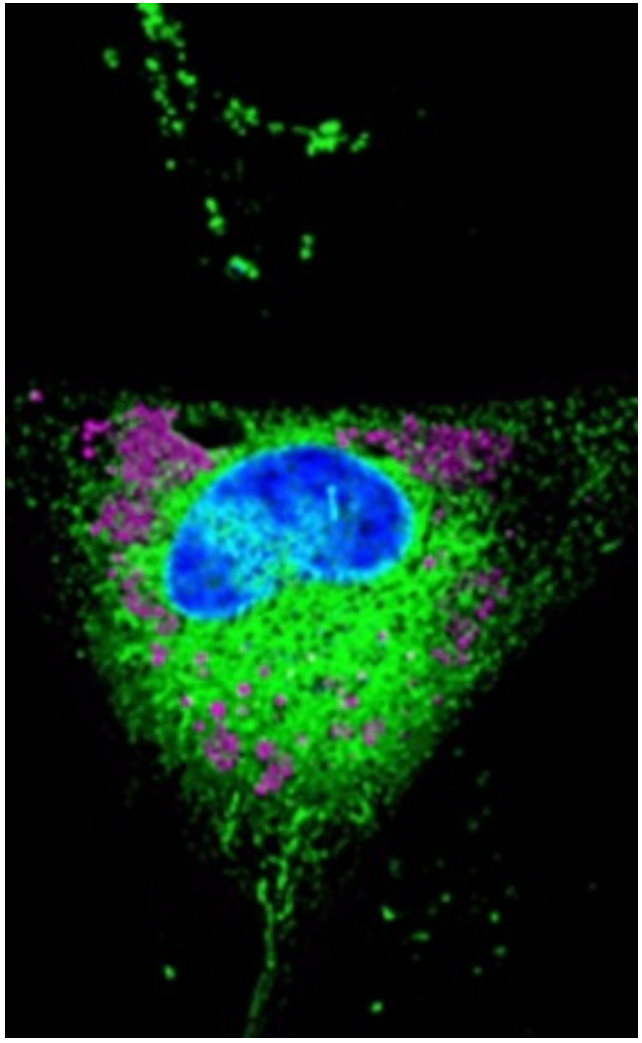
OPPORTUNITIES

- Genome Wide Association Studies (GWAS) looks for associations with SNPs and genetic factors across the whole genome to correlate with particular traits



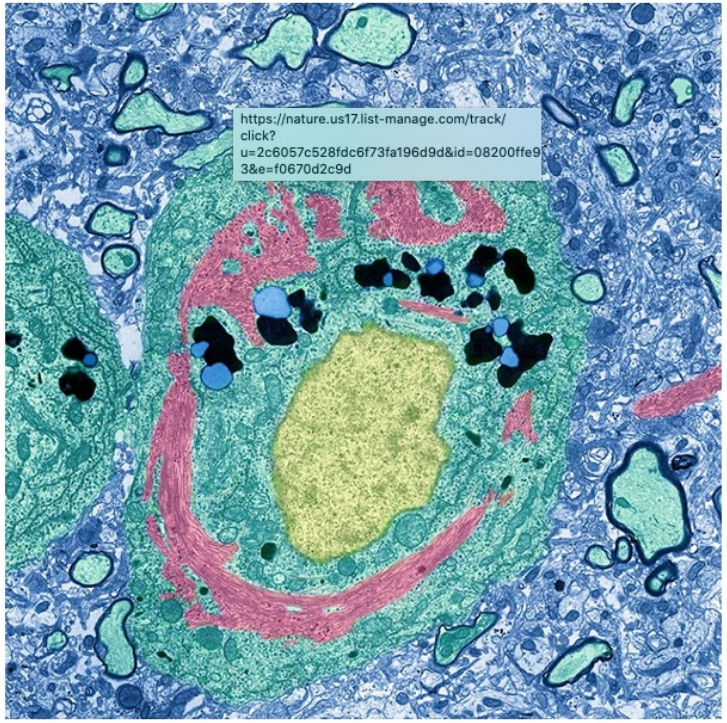
ApoE4 polymorphisms in lipid homeostasis of neurons and astrocyte who wants to know the presence of ApoE4 in her/his genotype ?

Certain genes can increase the risk of developing dementia, including Alzheimer's disease. One of the most significant genetic risk factors is a form of the *apolipoprotein E* gene called *APOE4*. About 25% of people carry one copy of *APOE4*, and 2 to 3% carry two copies. *APOE4* is the strongest risk factor gene for Alzheimer's disease, although inheriting *APOE4* does not mean a person will definitely develop the disease



Astrocyte assembly and secretion of triacylglycerol-rich lipoproteins, a process boosted by the APOE4 variant.

Lindner K. et al., 2022, Cell Reports 38, 110435



A neuron (green) from a person with Alzheimer's disease includes an unusual protein complex (pink) encircling the nucleus (yellow). (Thomas Deerinck, NCMIR/SPL)

How an Alzheimer's gene ravages the brain

No gene variant is a bigger risk factor for Alzheimer's disease than one called *APOE4*. But exactly how the gene spurs brain damage has been a mystery. A study has now linked *APOE4* with faulty cholesterol processing in the brain, which in turn leads to defects in the insulating sheaths that surround nerve fibres and facilitate their electrical activity. Preliminary results hint that these changes could cause memory and learning deficits. And the work suggests that drugs that restore the brain's cholesterol processing could treat the disease.

Nature | 4 min read

Reference: *Nature* paper

CoLaus : INFORMED CONSENT of adult population of Lausanne

Aller au site public

The last papers:

Antiochos P, Marques-Vidal P, McDaid A, Waeber G, Vollenweider P. **Association between parental history and genetic risk scores for coronary heart disease prediction: The population-based CoLaus study**. Atherosclerosis. 2016 Jan;244:59-65

Joost S, Duruz S, Marques-Vidal P, Bochud M, Stringhini S, Paccaud F, Gaspoz JM, Theler JM, Chételat J, Waeber G, Vollenweider P, Guessous I. **Persistent spatial clusters of high body mass index in a Swiss urban population as revealed by the 5-year GeoCoLaus longitudinal study**. BMJ Open. 2016 Jan 5;6(1):e010145

Le Boudec J, Marques-Vidal P, Cornuz J, Clair C. **Smoking**

Welcome to the CoLaus study website

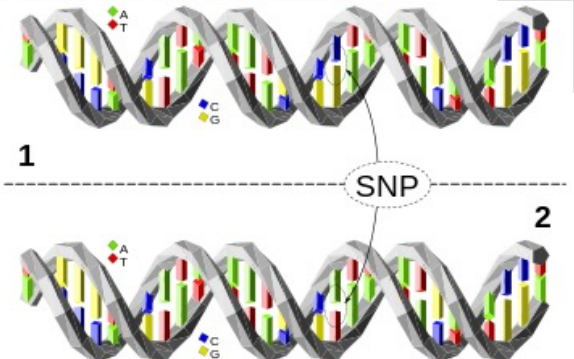
You will find here information on the **CoLaus | PsyCoLaus study** that started in Lausanne (Switzerland) in 2003. The main goals of this study are to obtain information on the epidemiology and genetic determinants of cardiovascular risk factors and diseases as well as mental health in the adult population of Lausanne.

Over 6'000 subjects have participated from 2003 to 2006 to the baseline assessment, and in 2009 we started our **first follow-up** including the entire cohort. Actually, more than 5'050 subjects have been already investigated in this follow-up.

You will find in these pages **a description of the different sub studies**.

For Reseachers

The investigators of CoLaus | PsyCoLaus welcome collaboration with other research groups. Collaboration helps to improve our knowledge of cardiovascular diseases and mental disorders, in terms of epidemiology, pathophysiology and genetics. Information to establish a collaboration are available here.



my life = my genome = my credit card = my future ?

personal data protection :
the *Personal Data Protection Act 2012*

The personal protection US act 2012 ethical issues

How does the Personal Data Protection Act work?

The PDPA will ensure a baseline standard of protection for personal data across the economy by complementing sector-specific legislative and regulatory frameworks. This means that organisations will have to comply with the PDPA as well as the common law and other relevant laws that are applied to the specific industry that they belong to, when handling personal data in their possession.

The PDPA takes into account the following concepts:

- Consent – Organisations may collect, use or disclose personal data only with the individual's knowledge and consent (with some exceptions);
- Purpose – Organisations may collect, use or disclose personal data in an appropriate manner for the circumstances, and only if they have informed the individual of purposes for the collection, use or disclosure; and
- Reasonableness – Organisations may collect, use or disclose personal data only for purposes that would be considered appropriate to a reasonable person in the given circumstances.

npj | Genomic Medicine

www.nature.com/npjgenmed

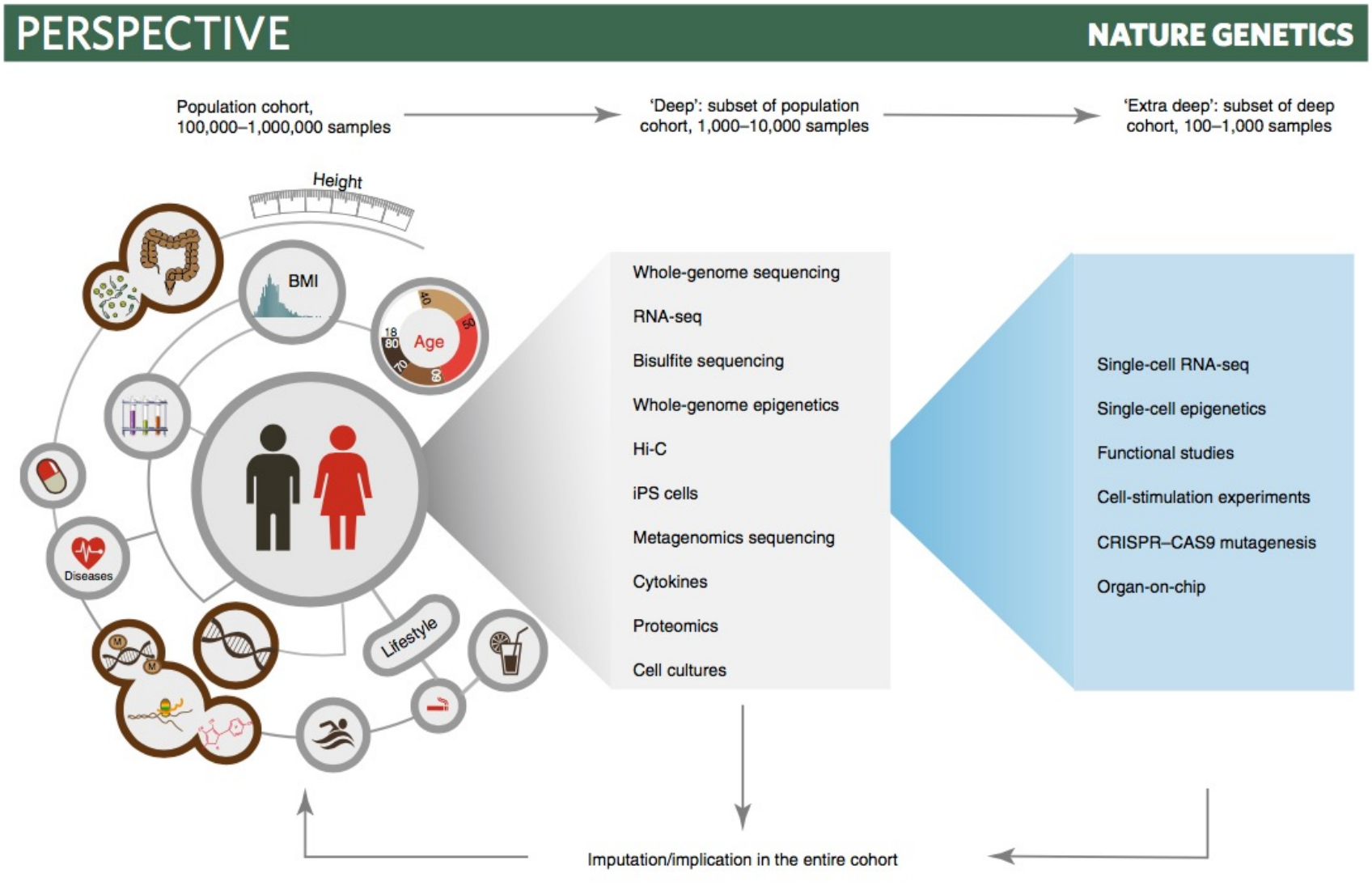
Genomic Medicine (2017)2:33 ; doi:10.1038/s41525-017-0036-1

PERSPECTIVE **OPEN**

A community effort to protect genomic data sharing, collaboration and outsourcing

Shuang Wang[1], Xiaoqian Jiang[1], Haixu Tang[2], Xiaofeng Wang[2], Diyue Bu[2], Knox Carey[3], Stephanie OM Dyke[4], Dov Fox[5], Chao Jiang[1], Kristin Lauter[6], Bradley Malin[7], Heidi Sofia[8], Amalio Telenti[9], Lei Wang[2], Wenhao Wang[2] and Lucila Ohno-Machado[1]

Advancing drug discovery : GWAS – cohort stratification



Wijmenga CV. 2018. Nature Genetics 50:322-328

GWAS - key concepts

- Mapping QTL (quantitative trait locus analysis) by association relies on linkage disequilibrium (LD) in the population
- LD can be caused by close linkage between a QTL and marker (= good) or by confounding between a marker and other effects (= usually bad);
- The power of QTL detection by LD depends on the proportion of phenotypic variance explained at a marker
- Mixed models are good for performing GWAS
- Genetic (co)variance can be estimated from GWAS summary statistics

GWAS timeline _ most diseases are of mulifactorial origins

EVER LARGER NUMBER OF GENETICAL MARKERS ASSOCIATED WITH DISEASES

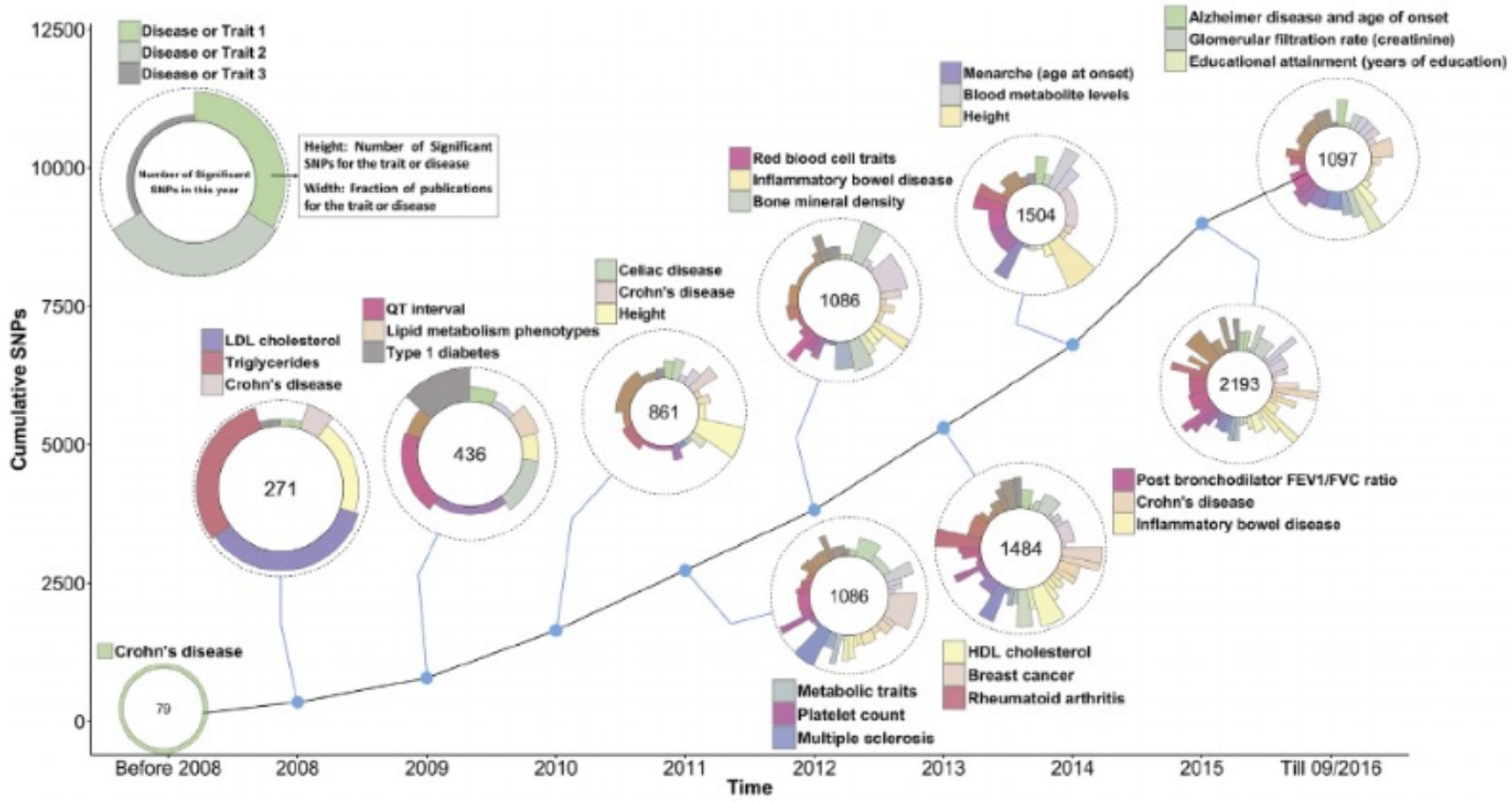
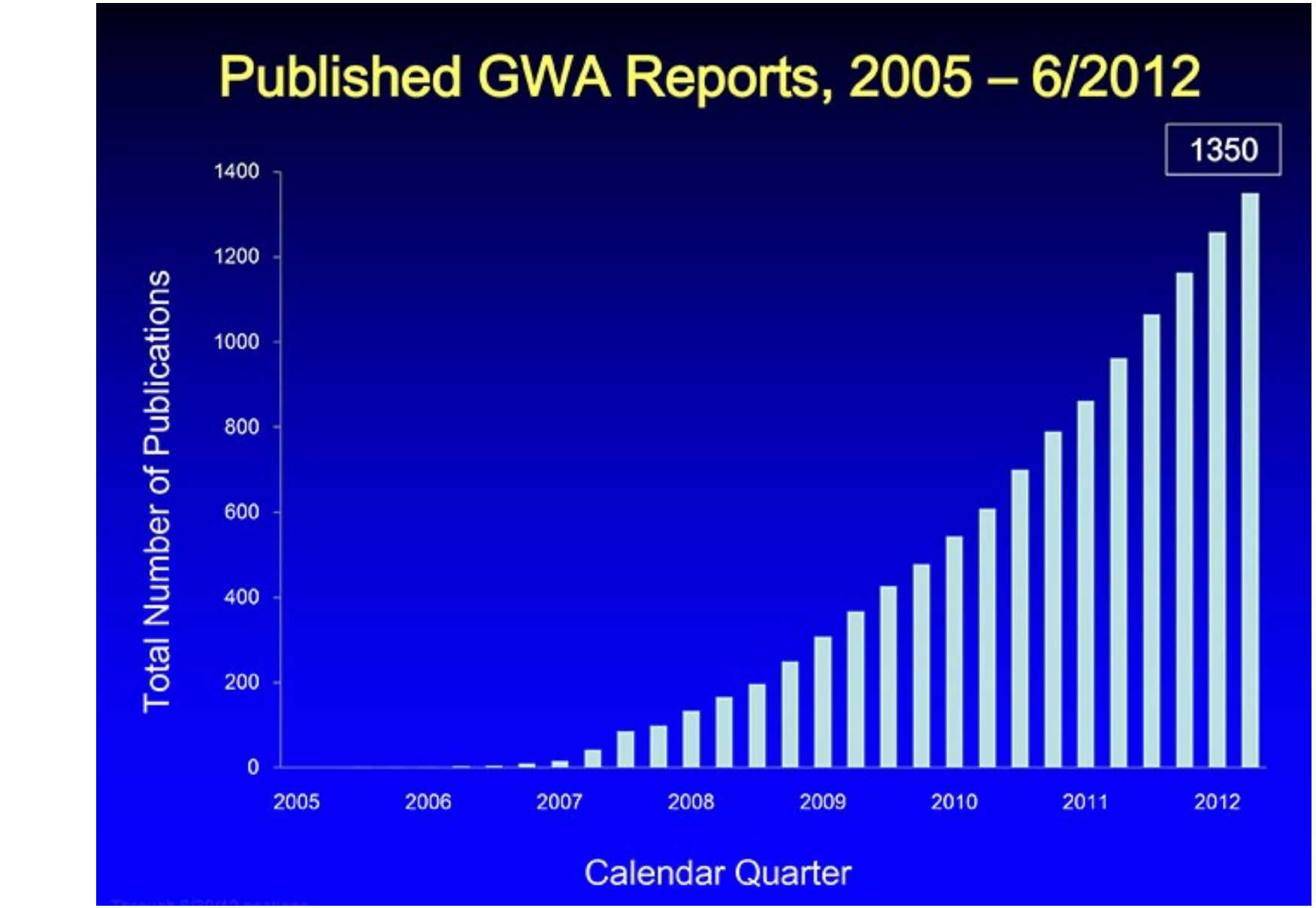


Figure 2. GWAS SNP-Trait Discovery Timeline

Visscher PM et al. 2017. Am. J. Human Genetics 101:5-22

GWAS reports _ leveling off : low hanging fruits gone ?

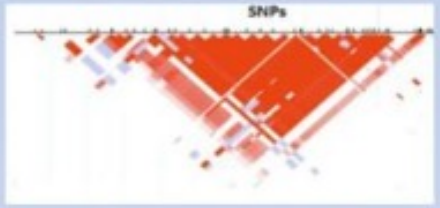


GWAS workflow

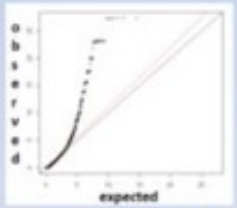
Large cohort (>1000) of cases and controls

Get genome information with SNP arrays

Find deviating from expected haplotypes
visualize SNP-SNP interactions using HapMap



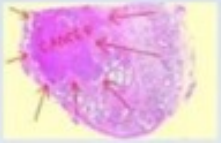
Detection of potential association signals and their fine mapping (e.g. detection of LD, stratification effect)



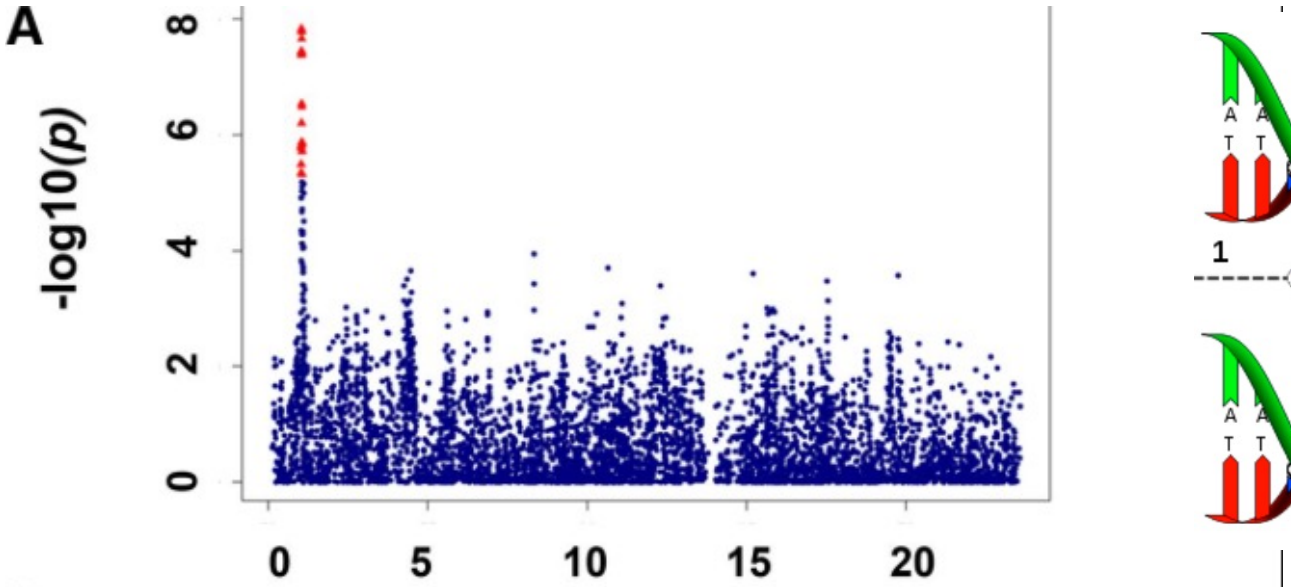
Replication of detected association in new cohot / subset for validation purposes

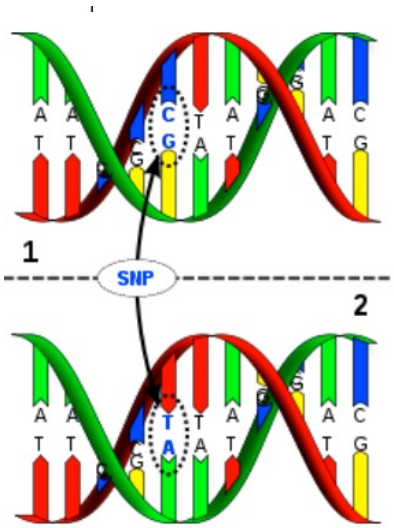
	AT	AG	Total
cases observed	35	65	100
contorls observed	125	25	100
Totals	160	90	200

Biological / clinical validation



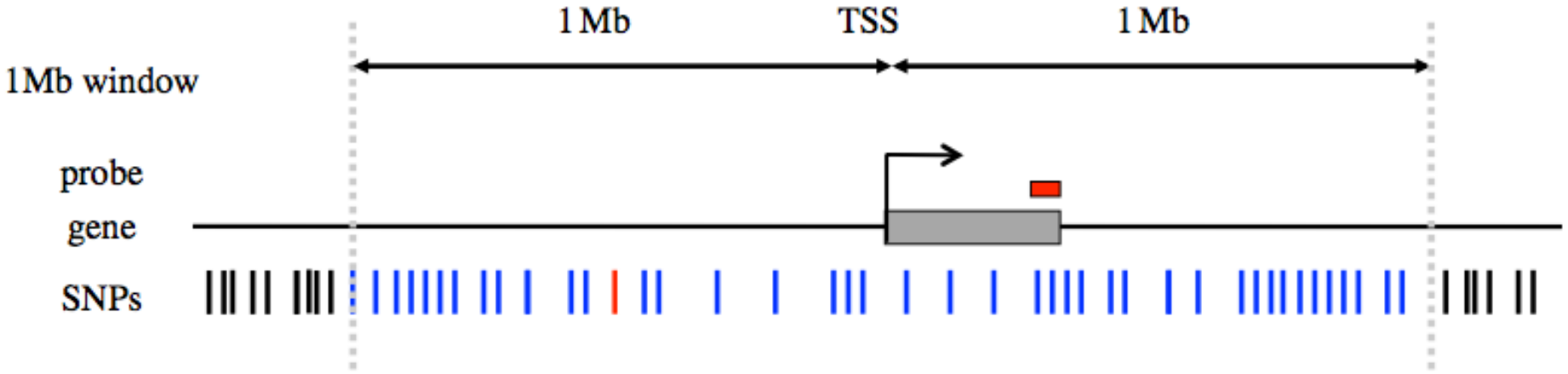
GWAS – probabilistic assessment and odds ratios over human 3.10^6 SNPs

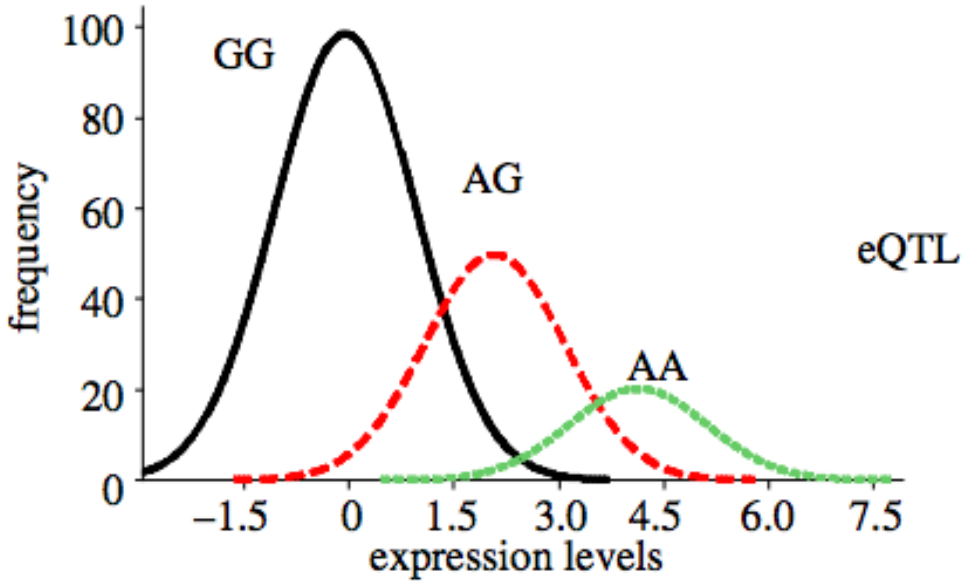




The National Human Genome Institute GWAS catalog (http://www.genome.gov/gwastudies) lists **over 3,600** SNPs identified for common diseases or traits, and in general, common diseases have multiple susceptibility alleles.

eQTL – trans and cis eQTL
Association of polymorphism with gene expression

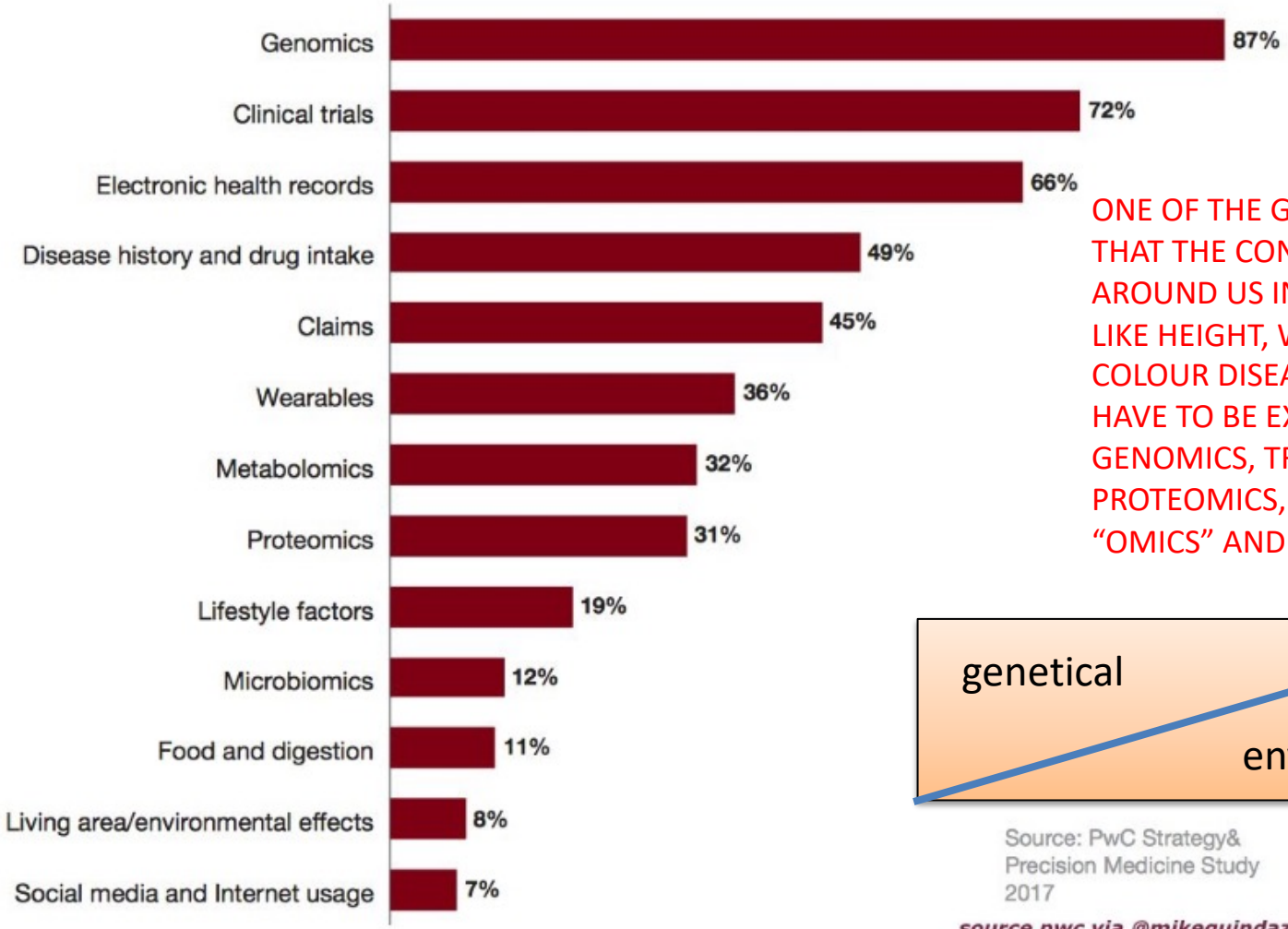


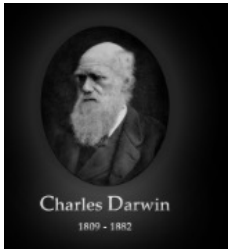


eg. analysis of one gene in multiple individuals)

PHC-precision medicine : relative contributions according to pwc

Exhibit 2
Most relevant data types for precision medicine



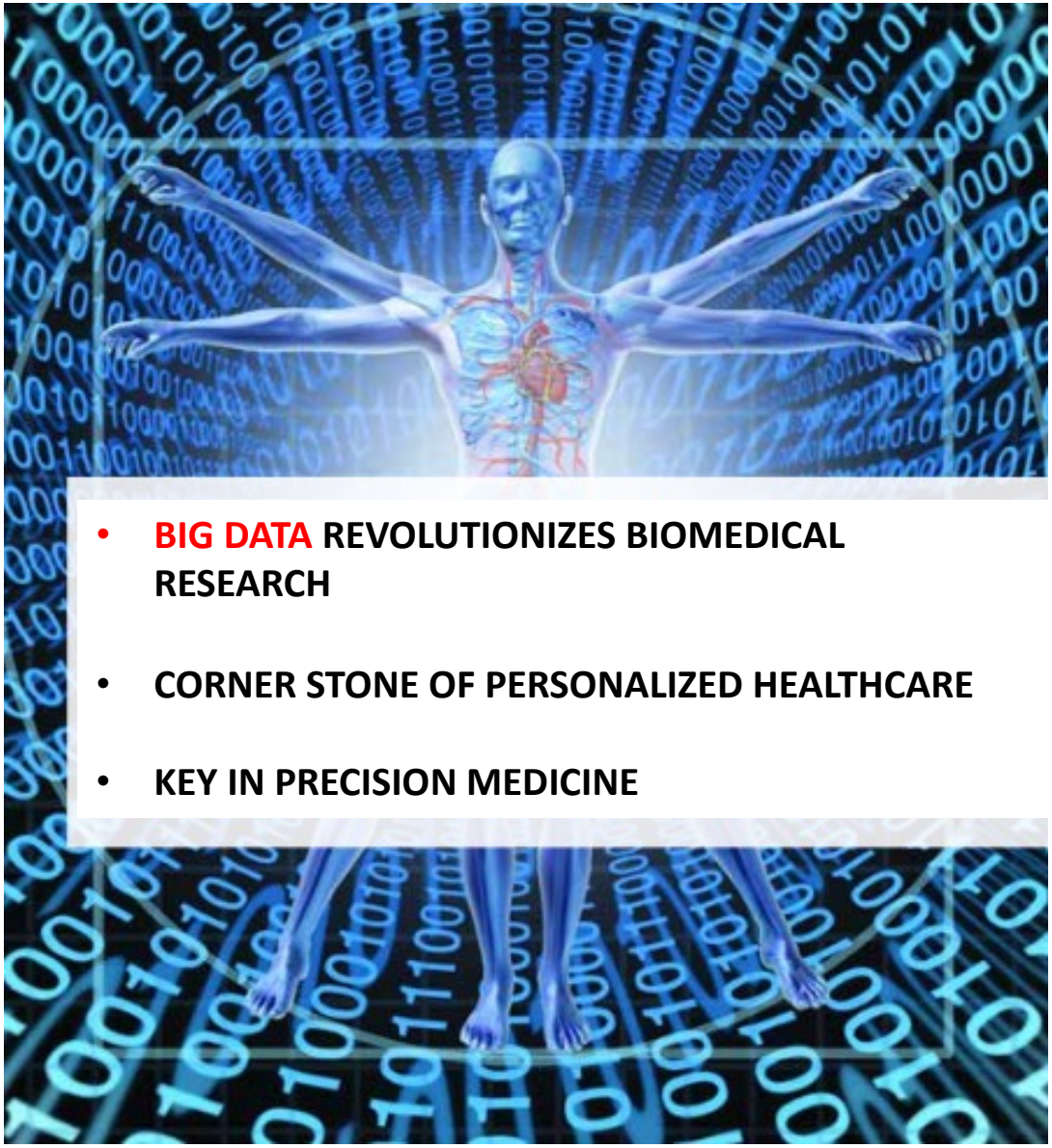


ONE OF THE GREAT CHALLENGE IS, THAT THE CONDITIONS WE SEE AROUND US IN THE REAL WORLD LIKE HEIGHT, WEIGHT, SKIN COLOUR DISEASE AND HEALTH, HAVE TO BE EXPLAINED BY GENOMICS, TRANSCRIPTOMICS, PROTEOMICS, METABOLOMICS, "OMICS" AND ENVIRONMENTAL

Source: PwC Strategy&
Precision Medicine Study
2017

source pwc via @mikequindazzi

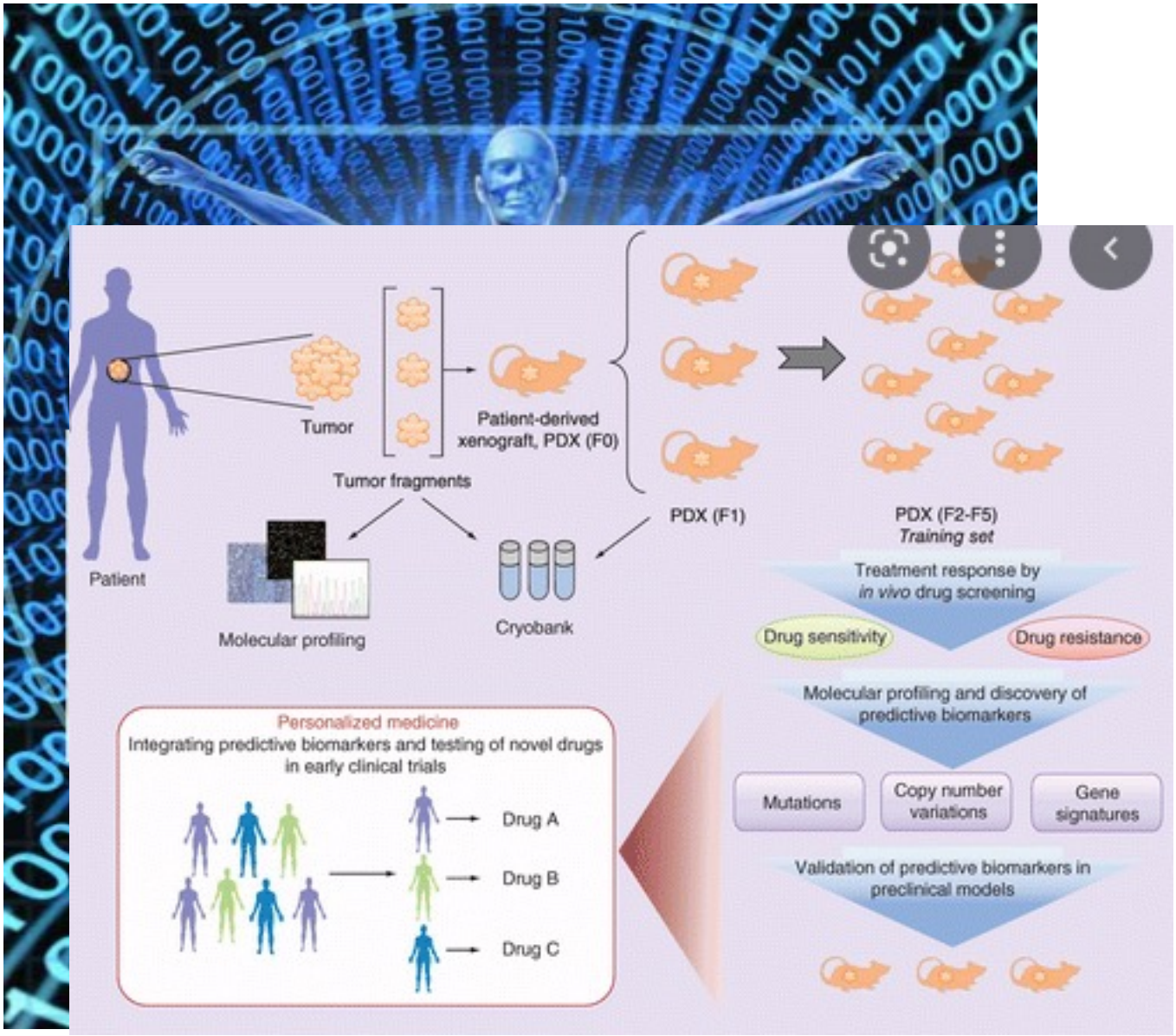
Big Data :
ultimate revolution in personalized healthcare



- **BIG DATA REVOLUTIONIZES BIOMEDICAL RESEARCH**
- **CORNER STONE OF PERSONALIZED HEALTHCARE**
- **KEY IN PRECISION MEDICINE**

- disease risk factors –
- disease enabling biomarkers
- imaging/histo pathology - pandemia
- patient genomics
- drug efficacy and safety
- machine learning precision diagnostic

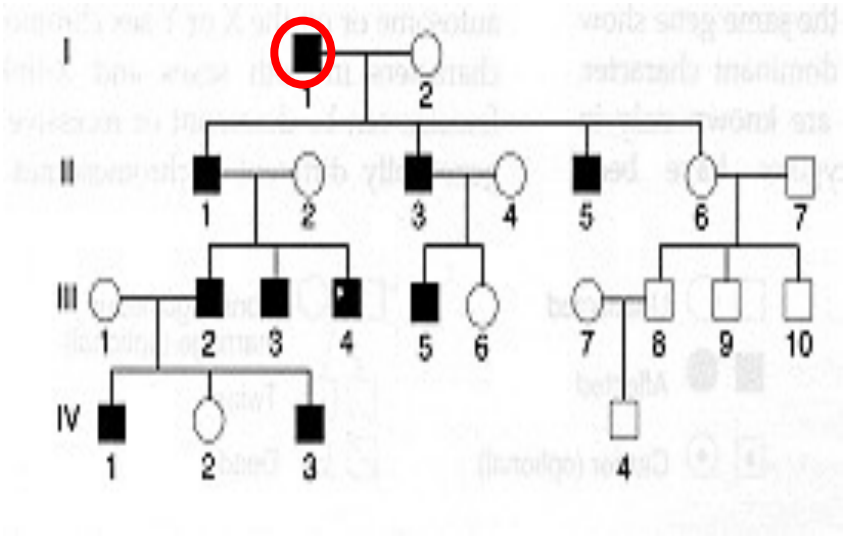
Patient derived tumors - a revolution in personalized healthcare



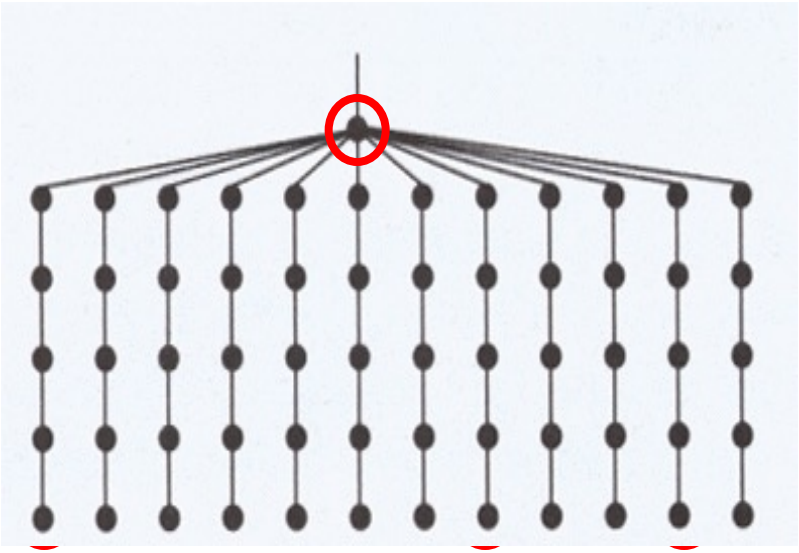
- Xenografts from individual patient tumors in immuno deficient animal pharmacological model
- Tailored made therapeutic medicines
- Tumor board

Linkage vs association

Linkage



Association



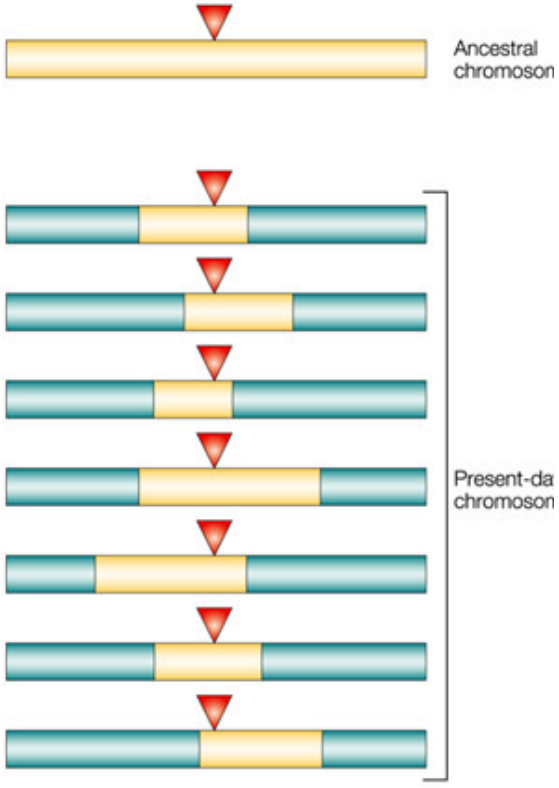
Families

pedigree, genealogy

Populations

statistical test on unrelated individuals

Linkage disequilibrium around an ancestral mutation : NL Svante Pääbo Neanderthalensis genome



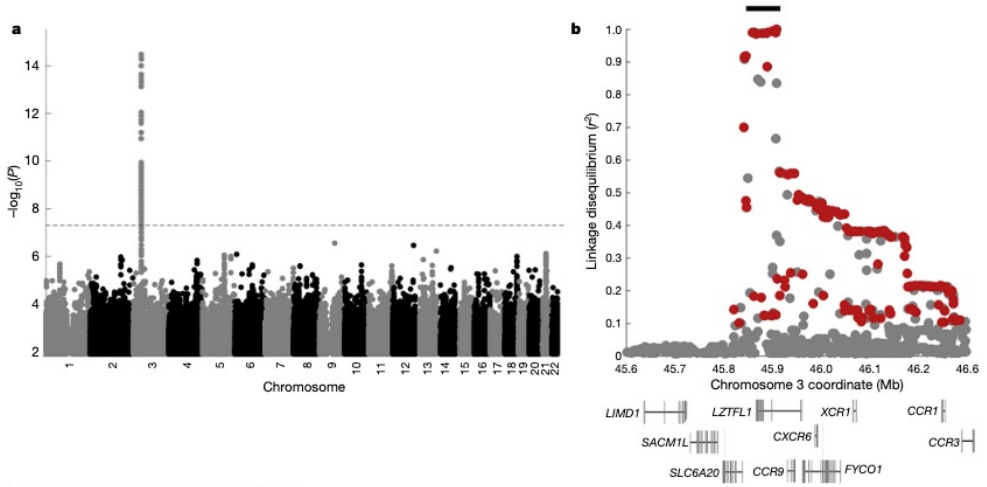
Article

The major genetic risk factor for severe COVID-19 is inherited from Neanderthals

https://doi.org/10.1038/s41586-020-2818-3
Received: 3 July 2020
Accepted: 22 September 2020
Published online: 30 September 2020
Check for updates

Hugo Zeberg[1,2]✉ & Svante Pääbo[1,3]✉

A recent genetic association study[1] identified a gene cluster on chromosome 3 as a risk locus for respiratory failure after infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A separate study (COVID-19 Host Genetics Initiative)[2] comprising 3,199 hospitalized patients with coronavirus disease 2019 (COVID-19) and control individuals showed that this cluster is the major genetic risk factor for severe symptoms after SARS-CoV-2 infection and hospitalization. Here we show that the risk is conferred by a genomic segment of around 50 kilobases in size that is inherited from Neanderthals and is carried by around 50% of people in south Asia and around 16% of



The genetic variants that are most associated with severe COVID-19 on chromosome 3 (45,859,651–45,909,024 (hg19)) are all in high linkage disequilibrium (LD)—that is, they are all strongly associated with each other in the population ($r^2 > 0.98$)—and span 49.4 thousand bases (kb) (Fig. 1b). This 'core' haplotype is furthermore in weaker link-

OVID-19. a, Manhattan plot talized patients with

Genomes Project. Red circles indicate genetic variants for which the alleles are correlated to the risk variant ($r^2 \geq 0.1$) and the risk alleles match the Vindija 33.19

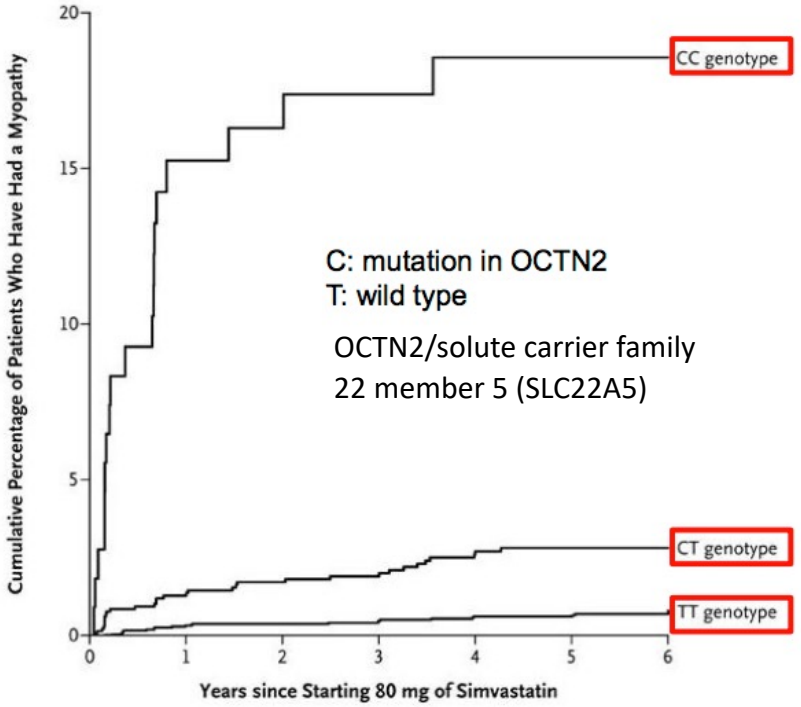
LD linkage desequilibrium

- Non-random association between alleles at different loci
- Many possible causes
  - mutation
  - drift / inbreeding / founder effects
  - population stratification
  - selection
- Broken down by recombination

GWAS – cadiomyocyte organic cation transporter OCTN2 and statin myopathies

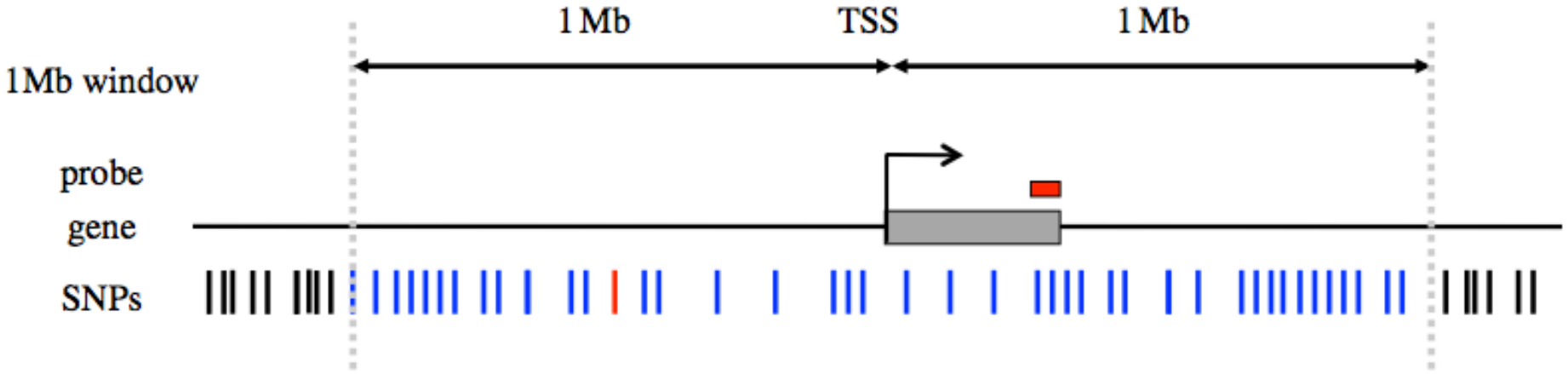
Myopathies associated with statins (HMGCoA inhibitors)

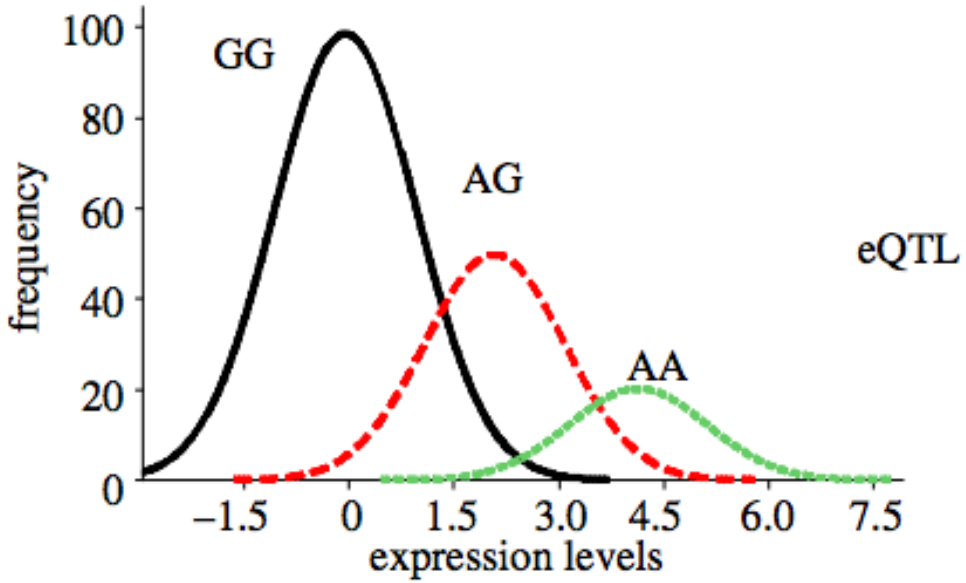
- 85 patients with myopathy and 90 controls (SEARCH Trial)
- All treated with 80 mg/d simvastatin
- Genome-wide association study for genetic risk factors for myopathy
- SNP rs4149056 is a good predictor for myopathy
- SNP rs4149056 is in the vicinity of OATP1B1, which carries statins into hepatocytes



N Engl J Med 2008;359:789-99

eQTL – trans and cis eQTL
Association of polymorphism with gene expression





eg. analysis of one gene in multiple individuals)

How pharmacogenetics CYP450 can change your life expectancy

WHY DOES SOMEONE NEED TWICE THE STANDART DOSE OF A DRUG FOR EFFICIENT TREATMENT ?

PERSONALIZED GENOMICS - when medicine/drug metabolites matters !

The *AmpliChip CYP450* test : a pharmacogenetic DNA oligonucleotide microarray screen to best individualize efficacy and safety of patients

- **each group of individuals do metabolize drugs differently; liver depending cytochrome CYP450‘s**

Three categories of individuals:

- **efficaceous metabolizers (EM)**
- **intermediary metabolizers (IM)**
- **poor metabolizers (PM)**

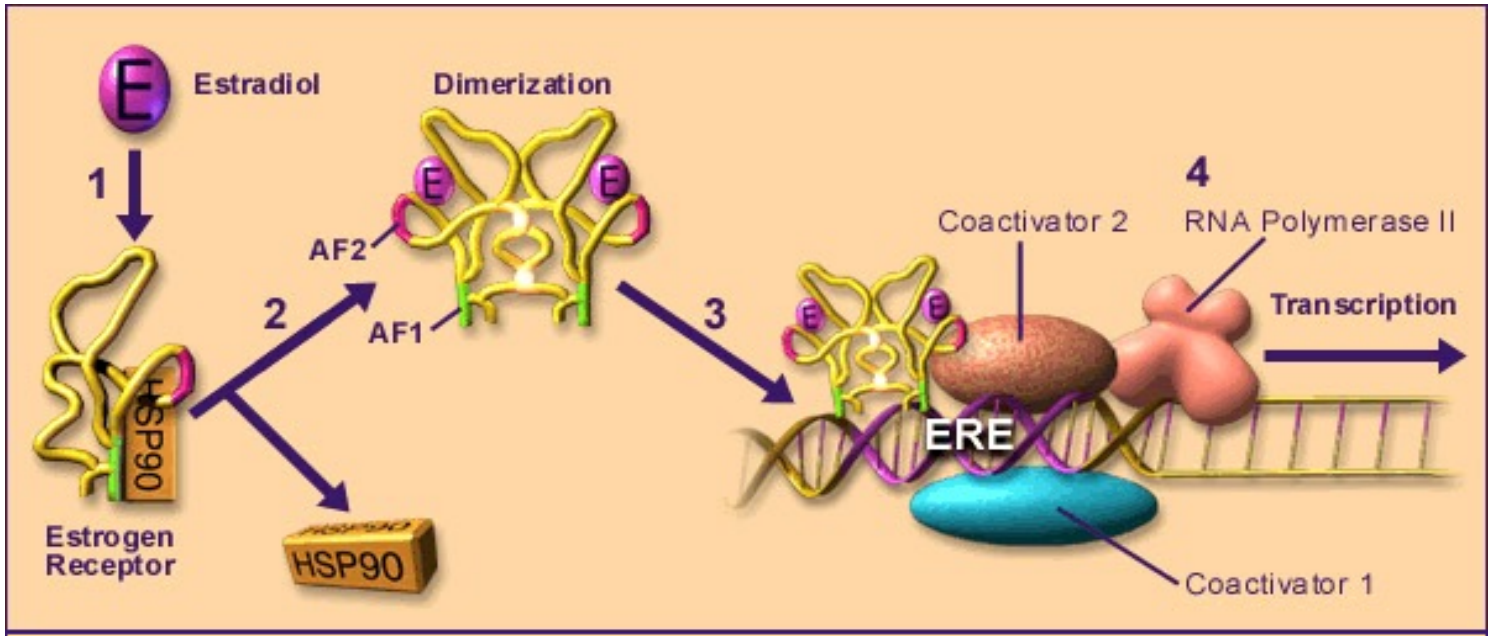
one of a few applications: genotyping of a women breast cancer patient allows to optimize her anti-hormonal therapy (dosis regimen) for potential relapse free survival

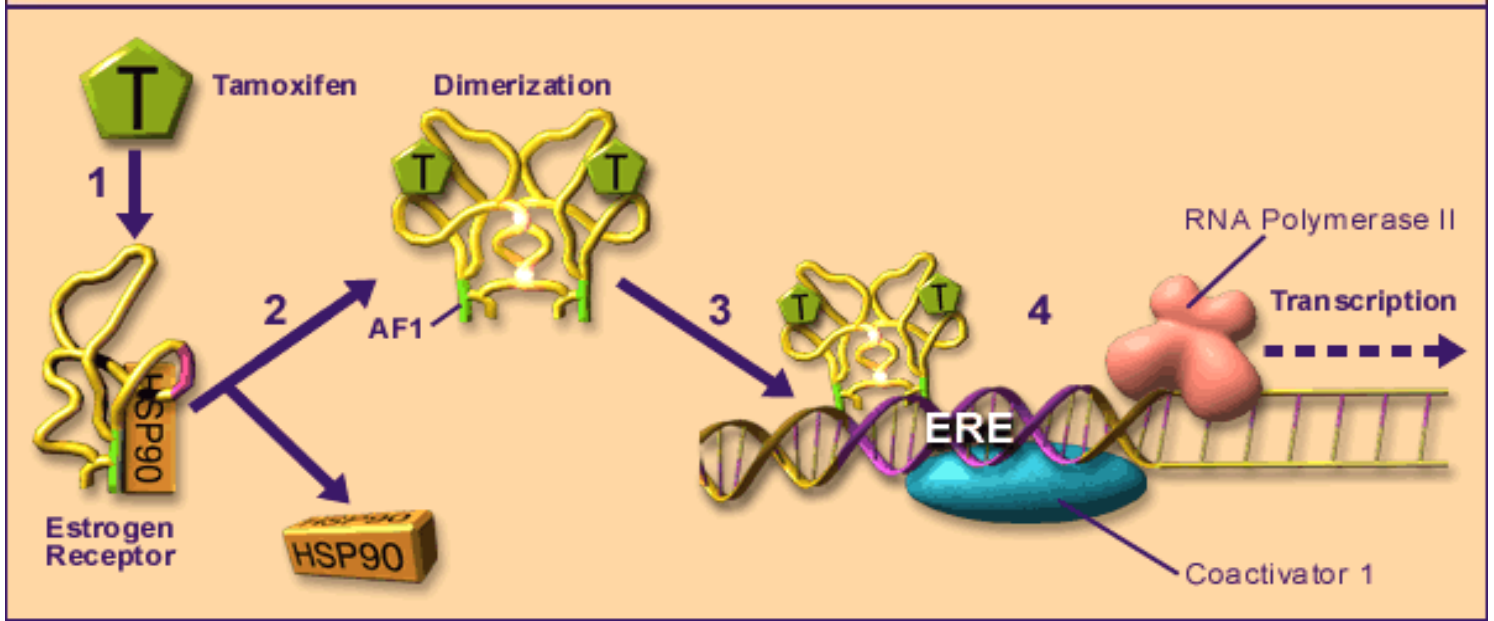
CYP2D6 allelic variants : pharmacogenetics_optimize the dose

Variantes alléliques	*Activité enzymatique* Mutation	Caucasiens	Noirs Africains	Est Asiatiques	Ethiopiens Saoudiens	Aborigènes Australiens
CYP2D6*4	*Enzyme inactive* Splicing défectueux 1846 G>A	**12-21%**	1-6%	1%	1-4%	1,5%
CYP2D6*5	*Pas d'enzyme* Délétion gène entier	2-7%	4-6%	6%	1-3%	7,5%
CYP2D6*10	*Enzyme instable* Pro34Ser, Ser486Thr	1-2%	4-6%	**33-51%**	3-9%	0,8%
CYP2D6*17	*Diminution affinité substrat* Thr107Ile, Arg296Cys, Ser486Thr	0%	**17-34%**	inconnu	3-9%	0,2%
CYP2D6*1xN* 2xN	*Activité enzymatique augmentée* (Multi) duplications	1-10%	1-3%	0-2%	**11-29%**	0%

Tableau 2. Fréquence des variantes alléliques et origine ethnique.
(Données compilées et tirées des réf. 2,5,29-39).

Tamoxifen _ co regulator swapping on ERalpha

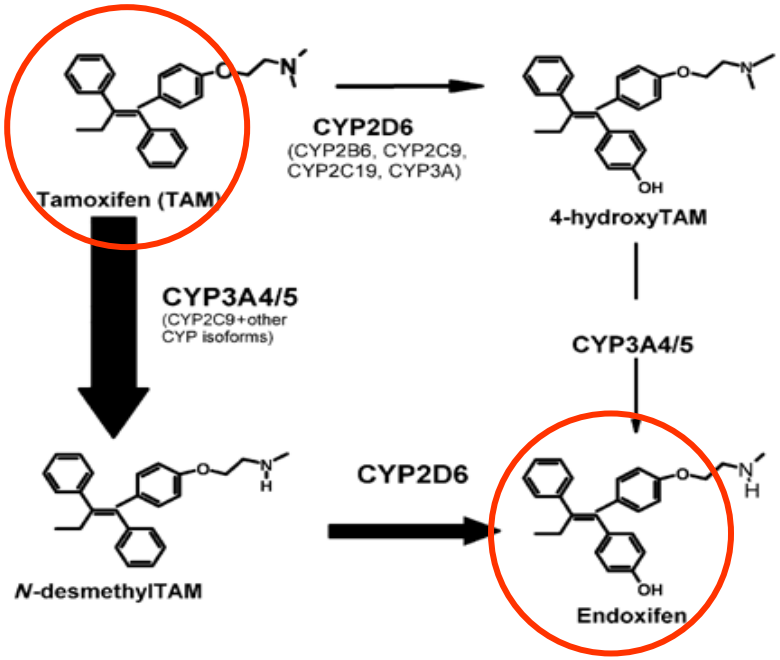


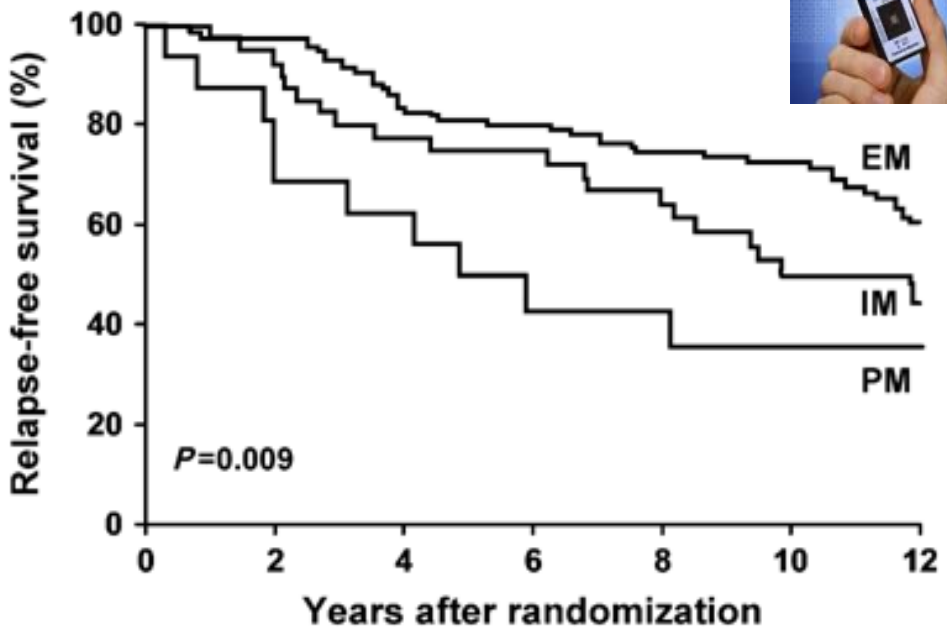


Pharmacogenetics - optimize the dose !

- Tamoxifen or TAM (partial ERα agonist) works as prodrug: its metabolite (Endoxifen) is the active principle when administered *per os*

- Endoxifen works anti proliferative on the mammary gland
- Cytochrome CYP2D6 as critical step in the metabolization of TAM into Endoxifen
- <u>CYP2D6 polymorphism</u> analysis allows an optimal invidualized therapy



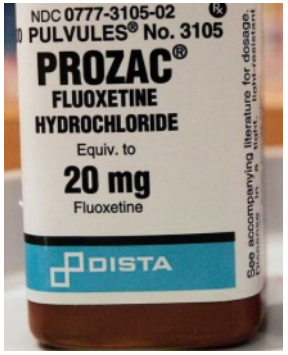


Personalized therapy : check BBB transporter status of patient

Neuron 57, 203–209, January 24, 2008 ©2008 Elsevier Inc.

Neuron

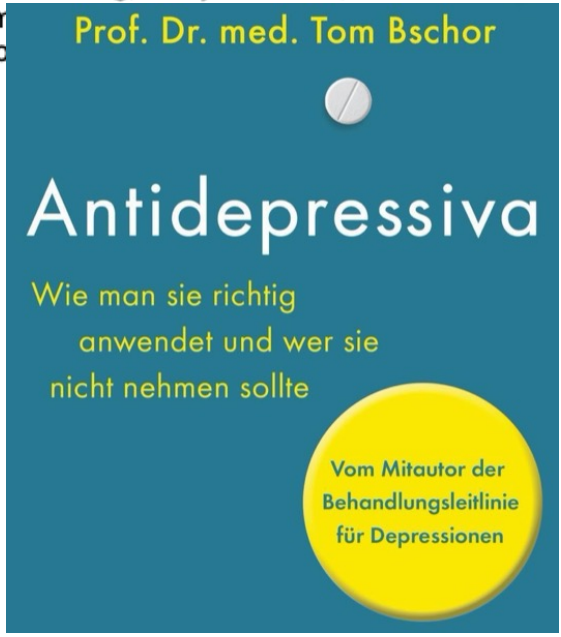
Clinical Study



Polymorphisms in the Drug Transporter Gene *ABCB1* Predict Antidepressant Treatment Response in Depression

Manfred Uhr,[1,*] Alina Tontsch,[1] Christian Namendorf,[1] Stephan Ripke,[1] Susanne Lucae,[1] Marcus Ising,[1] Tatjana Dose,[1] Martin Ebinger,[1] Marcus Rosenhagen,[1] Martin Kohli,[1] Stefan Kloiber,[1] Daria Salyakina,[1] Thom
Michael Specht,[1] Benno Pütz,[1] Elisabeth B. Binder,[1] Bertram Müller-Myhsok,[1] and Florian Ho
[1]Max Planck Institute of Psychiatry, Kraepelinstr. 10, 80804 Munich, Germany
*Correspondence: uhr@mpipsykl.mpg.de
DOI 10.1016/j.neuron.2007.11.017

- Tool to reduce over- and under-dosing
- Estimated 20% reduction in adverse events



Pharmacogenetics - optimize the dose !

The knowledge of pharmacogenomics of *CYP2D6* in medicine treatment is increasing, and it can be used for the development of

PERSONALIZED MEDICATION in term of genetic-based dosing recommendation

Table 1

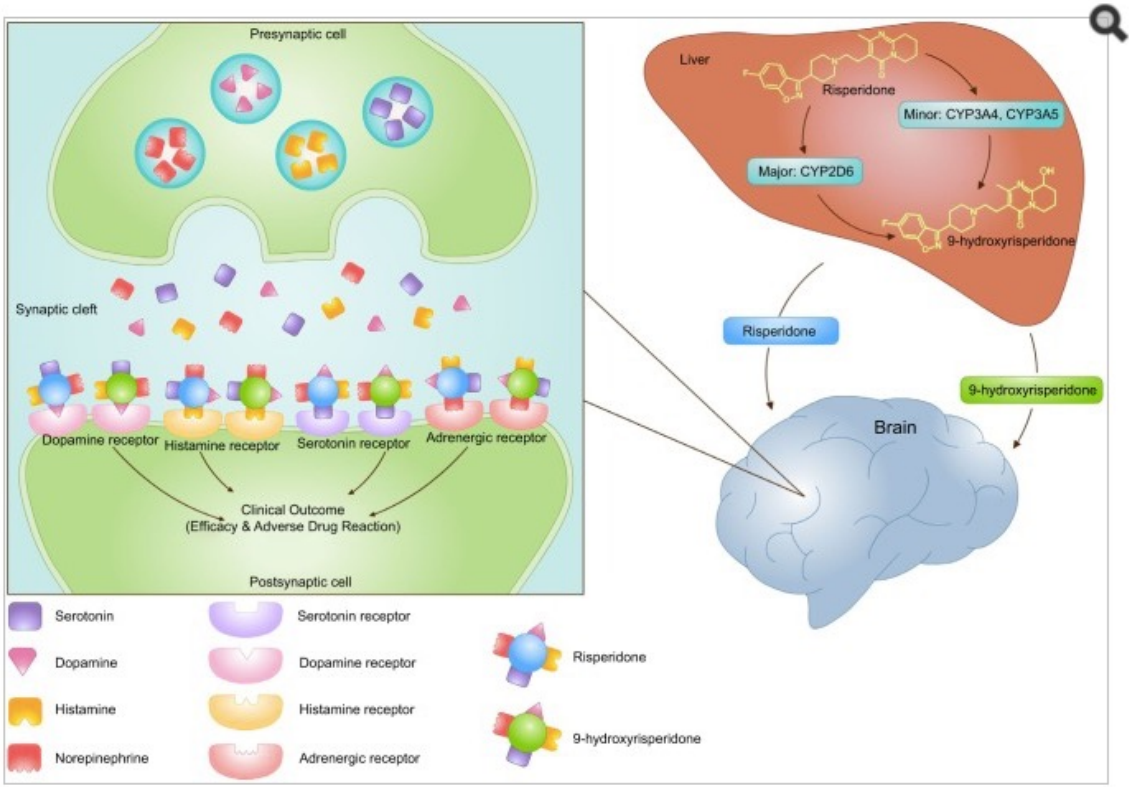
Clinically relevant drug substrates for metabolism by CYP2D6 enzymes

CYP2D6 substrates					
Antidepressants	**Beta blockers**	**Anti-cancer**	**Antipsychotics**		
Amitriptyline	Alprenolol	Tamoxifen	Haloperidol	Mexiletine	Methoxyamphetamine
Clomipramine	Carvedilol		Perphenazine	Minaprine	Bufuralol
Desipramine	Propafenone		Risperidone	Nebivolol	Chlorpheniramine
Imipramine	Bupranolol		Thioridazine	Nortriptyline	Chlorpromazine
Fluoxetine	Clonidine		Zuclopenthixol	Ondansetron	Clonidine
Paroxetine	Debrisoquine		Atomoxetine	Oxycodone	Codeine
Tamoxetine	Metoprolol		Alprenolol	Perhexiline	Debrisoquine
Trimipramine	Propranolol		Amphetamine	Phenacetin	Dexfenfluramine
Venlafaxine	Timolol		Aripiprazole	Phenformin	Dextromethorphan

Psychotherapy : pharmacogenetics_optimize the dose

The knowledge of pharmacogenomics of *CYP2D6* in risperidone treatment is increasing, and it can be used for the development of PERSONALIZED MEDICATION in term of genetic-based dosing recommendation !

Figure 1



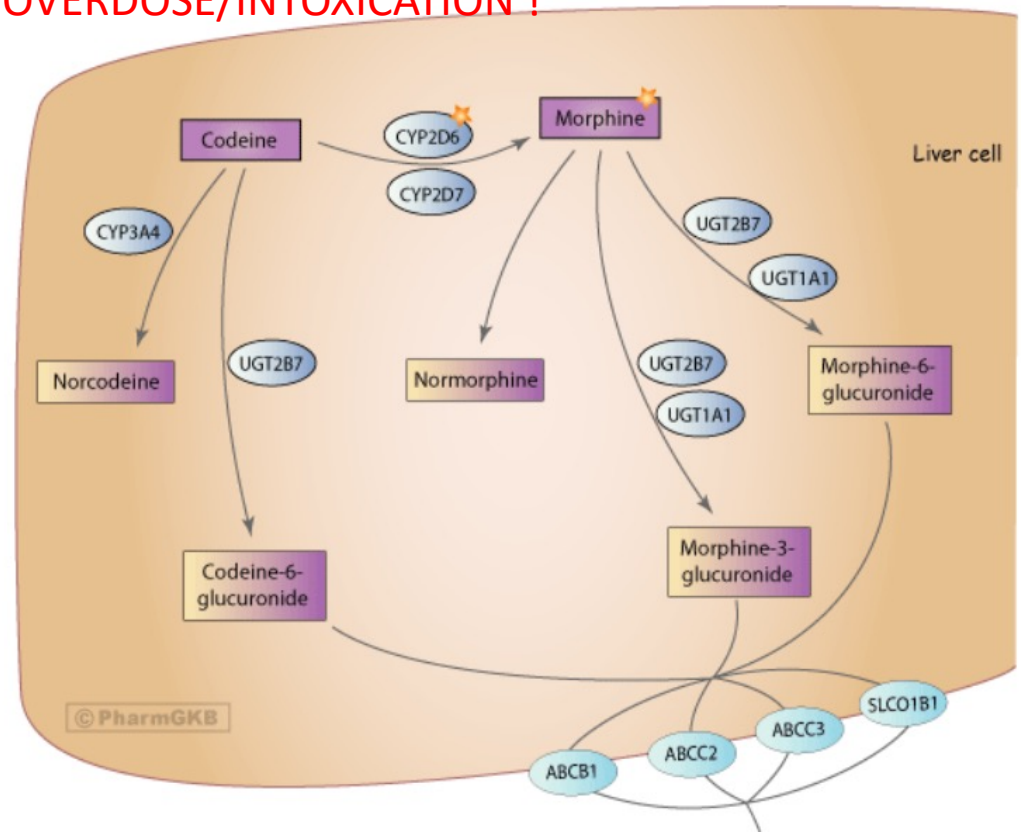
The pathway for pharmacokinetics and pharmacodynamics of risperidone.

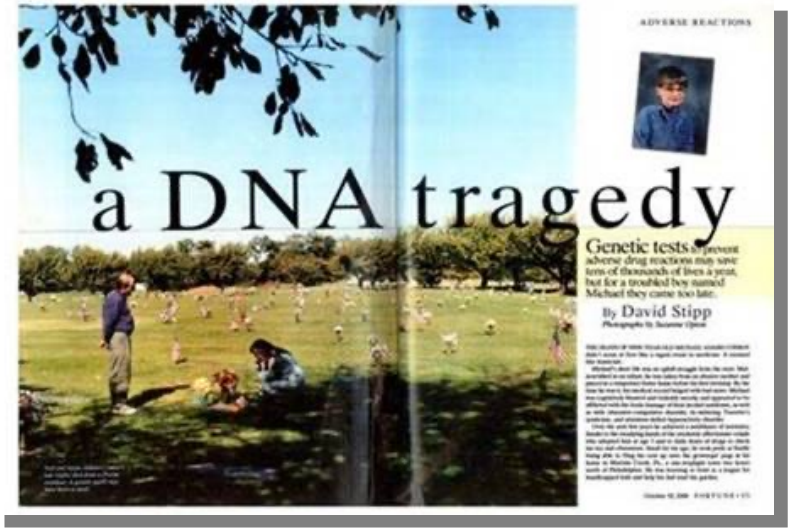
RISPERIDONE IS AN ATYPICAL ANTIPSYCHOTIC (AAP) DRUG THAT IS BEING PRESCRIBED FOR THE TREATMENT OF IRRITABILITY OR AGGRESSION IN AUTISM, SCHIZOPHRENIA, AND ACUTE BIPOLAR MANIA. RISPERIDONE EXERTS ITS PHARMACOLOGIC EFFECTS BY BINDING TO AND INHIBITING HIGH-AFFINITY SEROTONIN AND DOPAMINE RECEPTORS.

Pharmacogenomics and Personalized Medicine (2016) 9: 131–147

Pharmacogenetics : metabolism of codeine and morphine

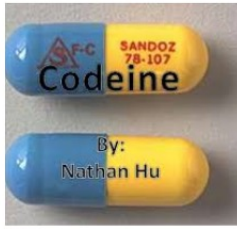
RAPID EFFICIENT CODEINE METABOLIZER SUBJECTS HAVE EXPERIENCED MORPHINE OVERDOSE/INTOXICATION !

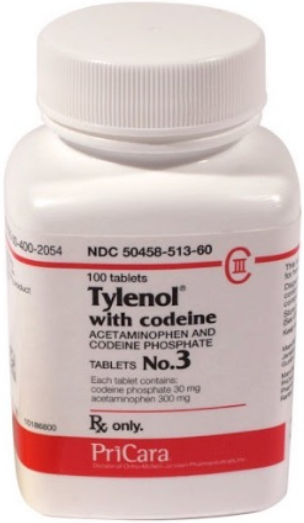




Polymorphism categories of CYP2D6 individuals:

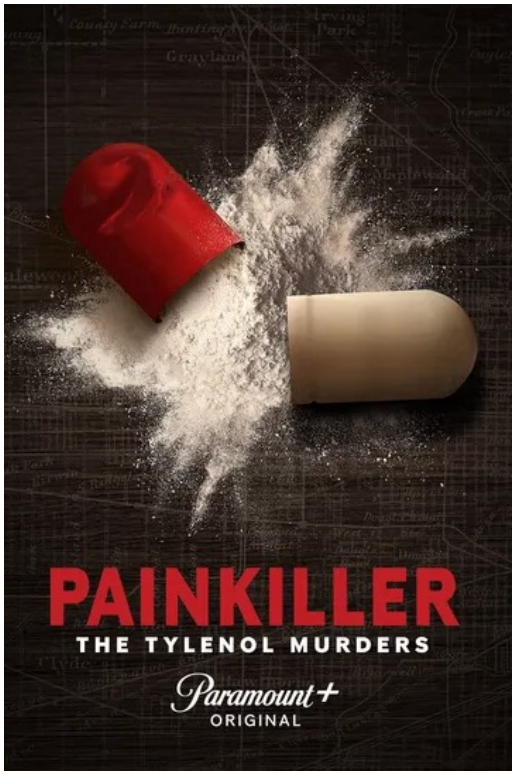
- **efficaceous metabolizers (EM)**
- **intermediary metabolizers (IM)**
- **poor metabolizers (PM)**

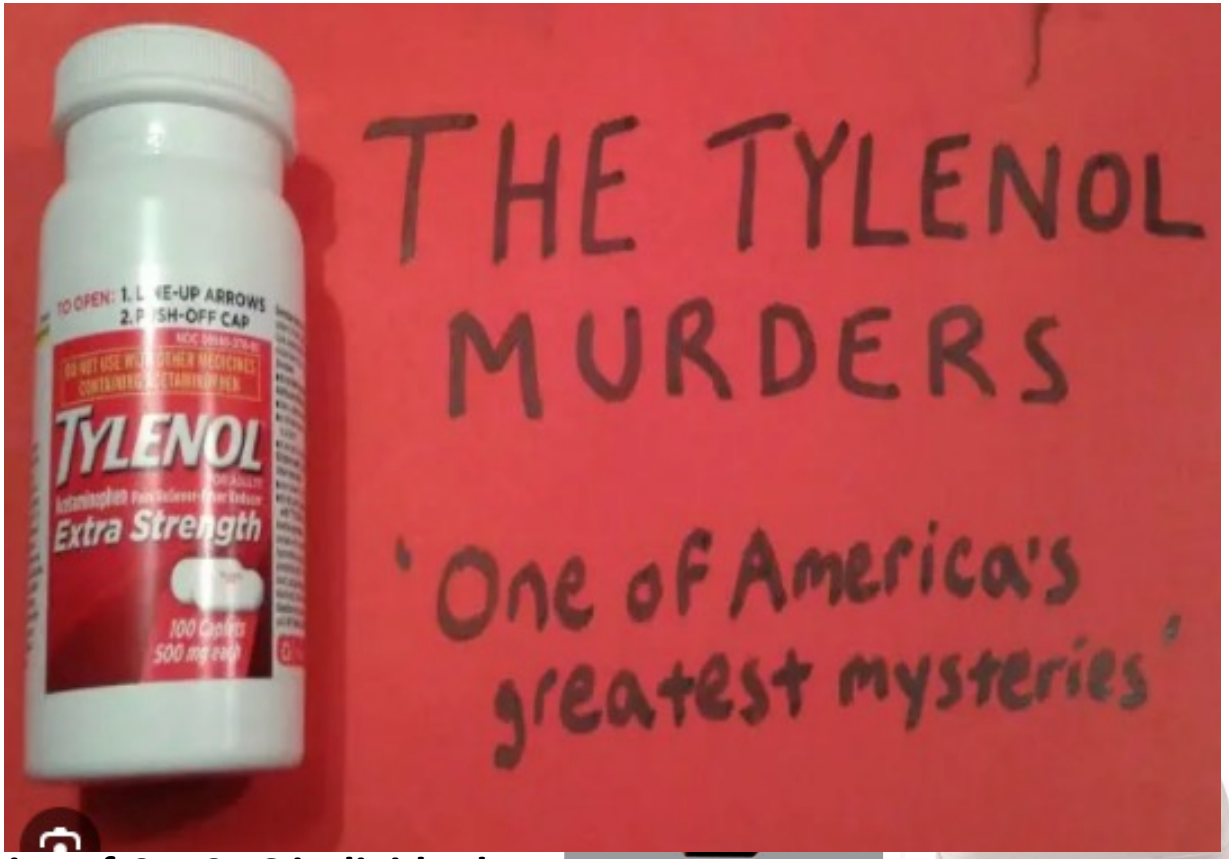




Pharmacogenetics in the press : metabolism of codeine and morphine

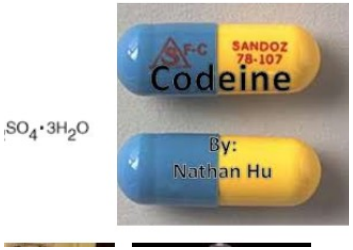
RAPID EFFICIENT CODEINE INTO MORPHINE METABOLIZER SUBJECTS HAVE EXPERIENCED MORPHINE OVERDOSE INTOXICATION !

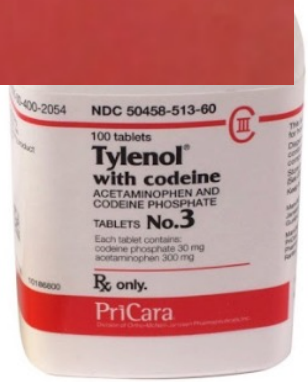




Polymorphism categories of CYP2D6 individuals:

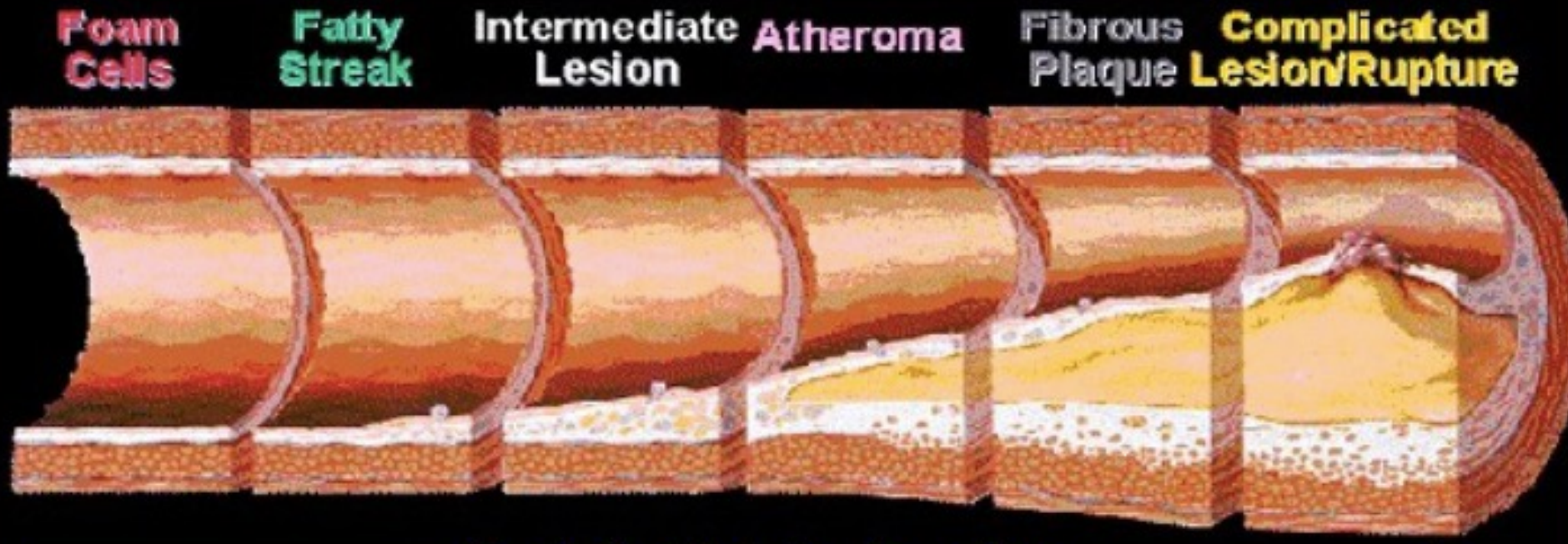
- **efficaceous metabolizers (EM)**
- **intermediary metabolizers (IM)**
- **poor metabolizers (PM)**





ATHEROSCLEROSIS

Atherosclerosis Timeline

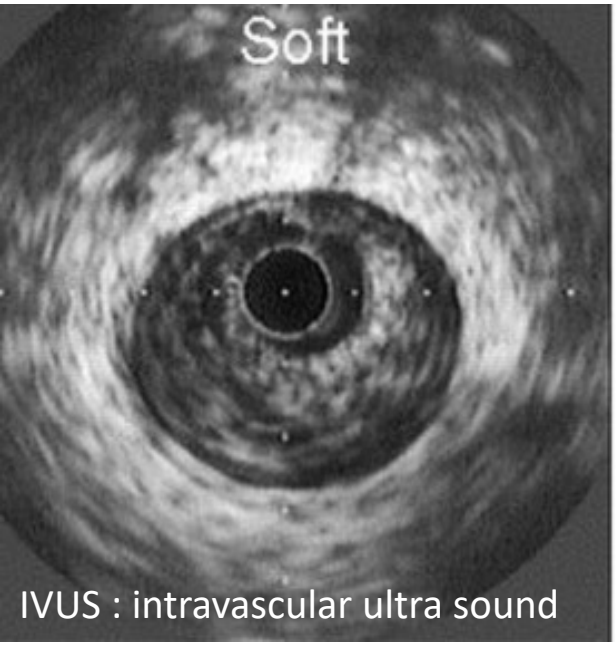


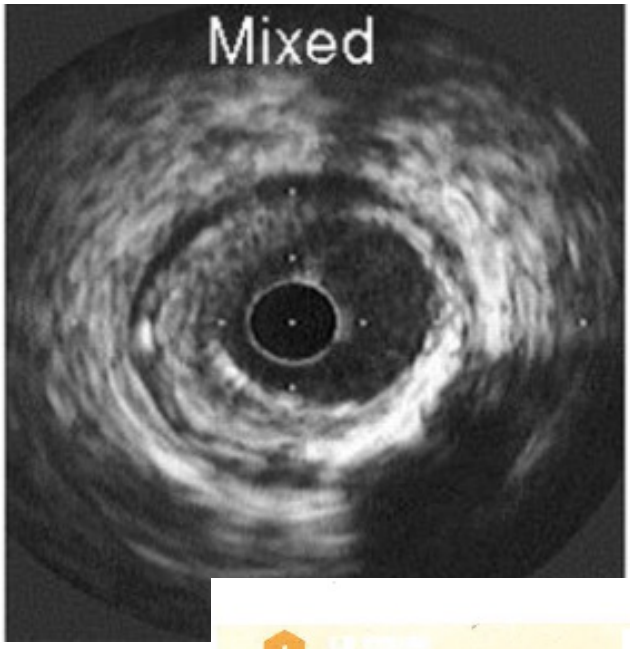
Endothelial dysfunction

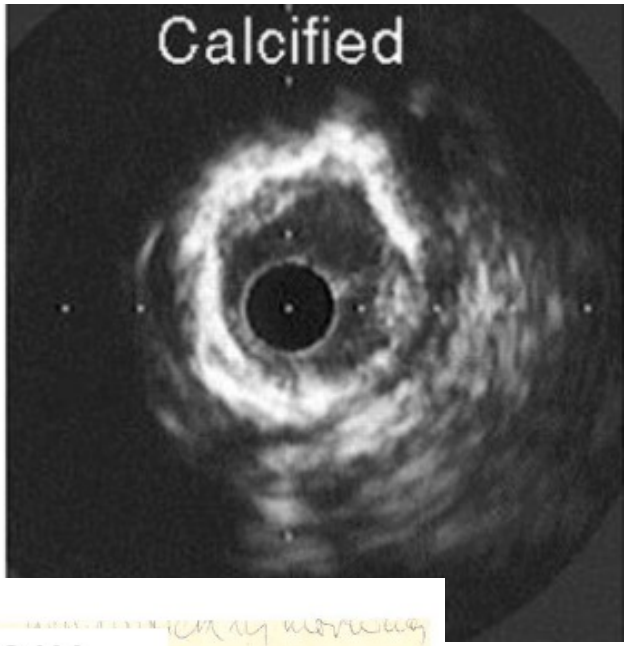
From first decade | From third decade | From fourth decade

Growth mainly by lipid accumulation | Smooth muscle and collagen | Thrombosis, hematoma

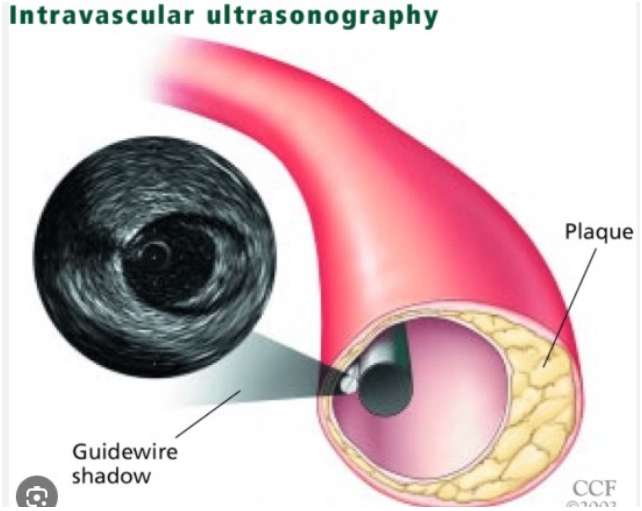
IVUS : looking inside the –coronary- arteries

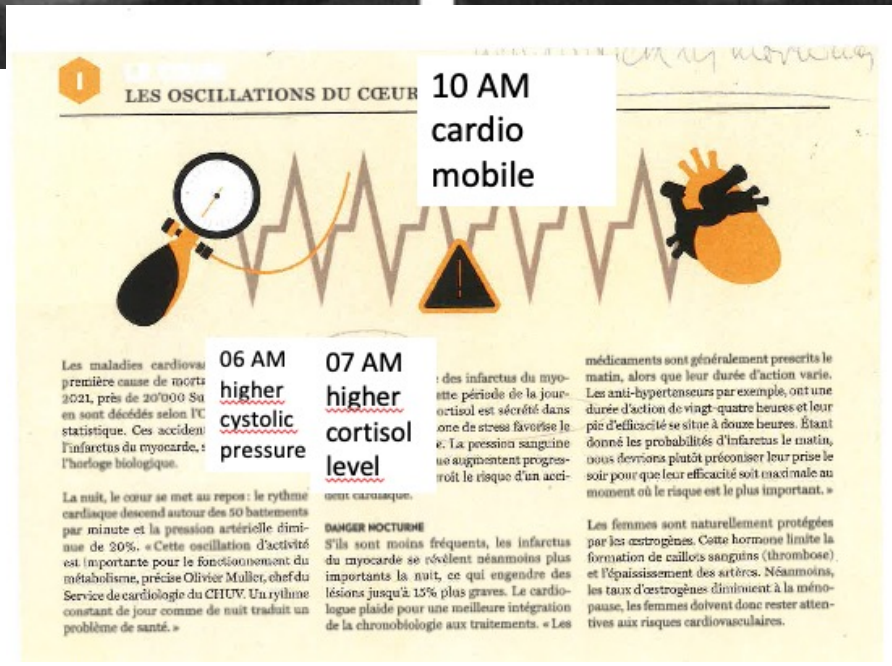






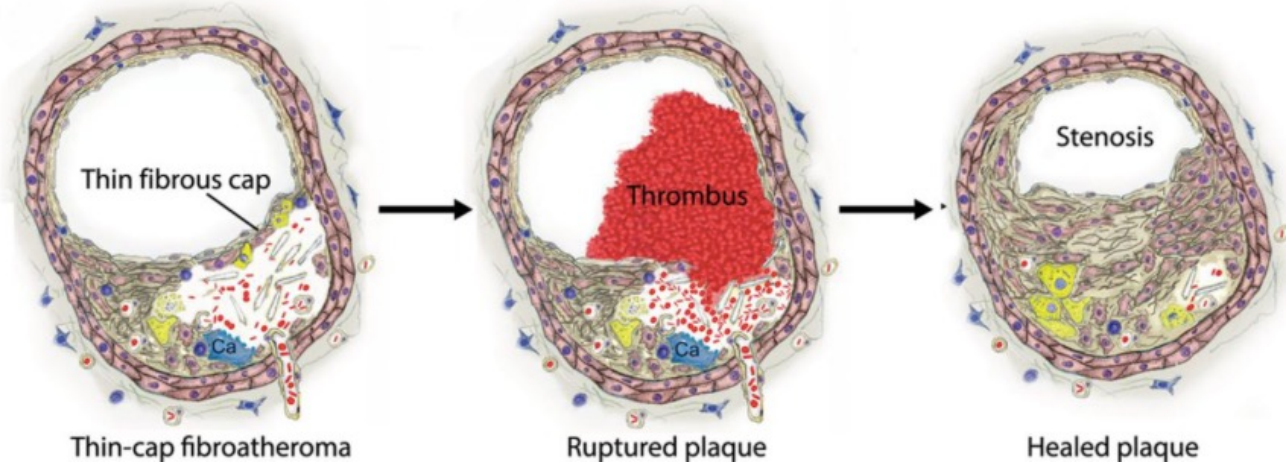
IVUS : intravascular ultra sound



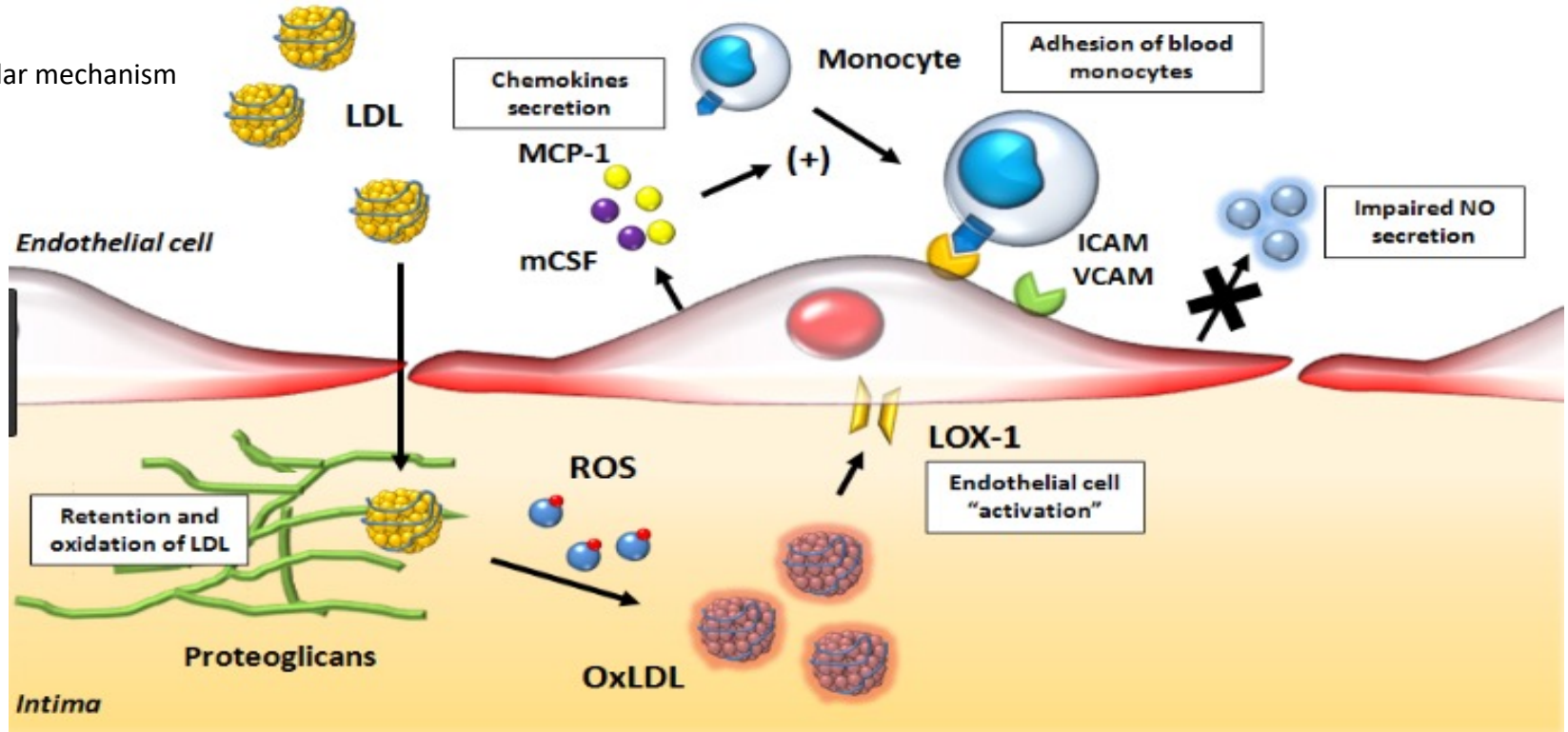


Stroke and acute heart failure : the unstable atheroma plaque

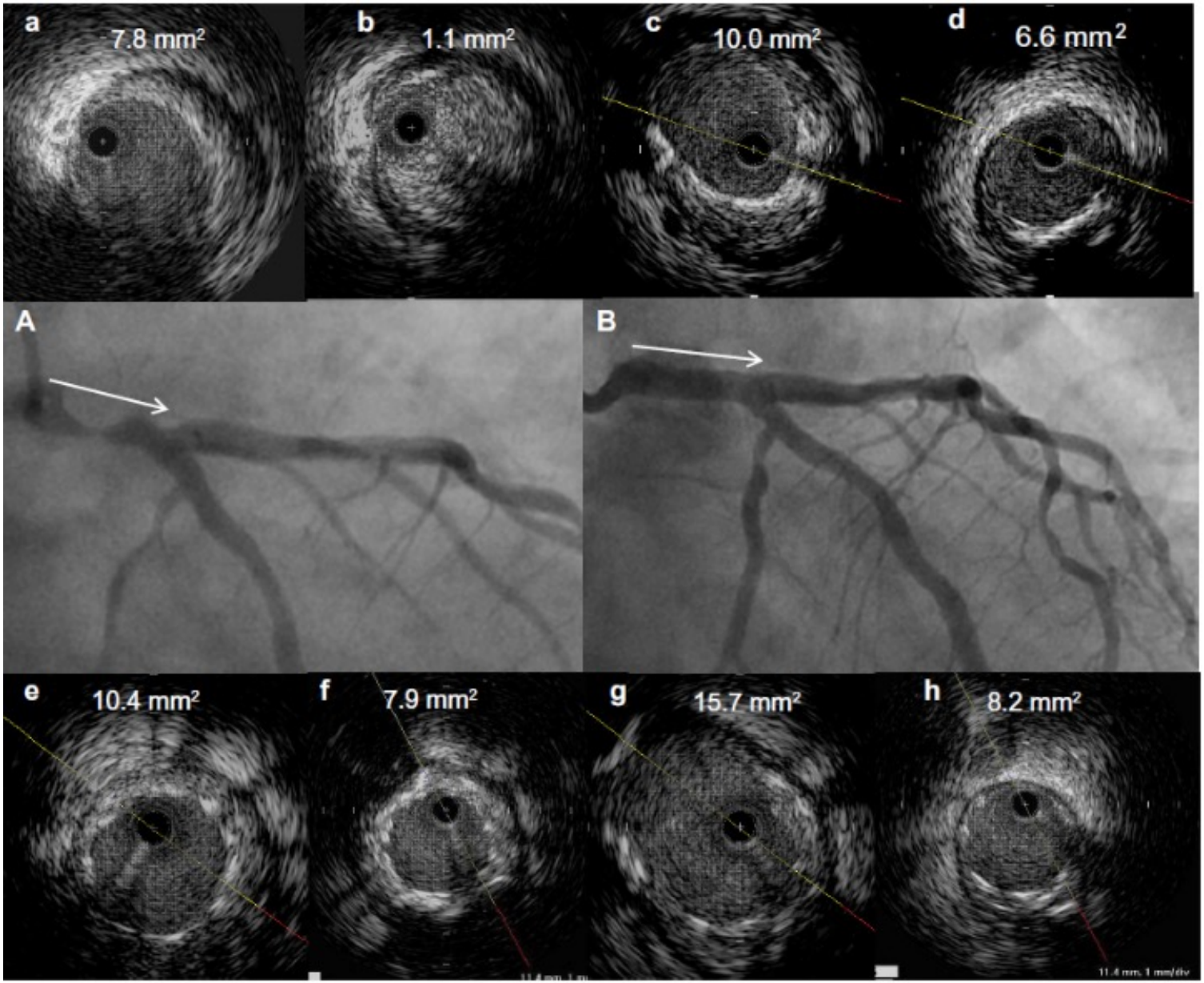
at histopathological level



at molecular mechanism



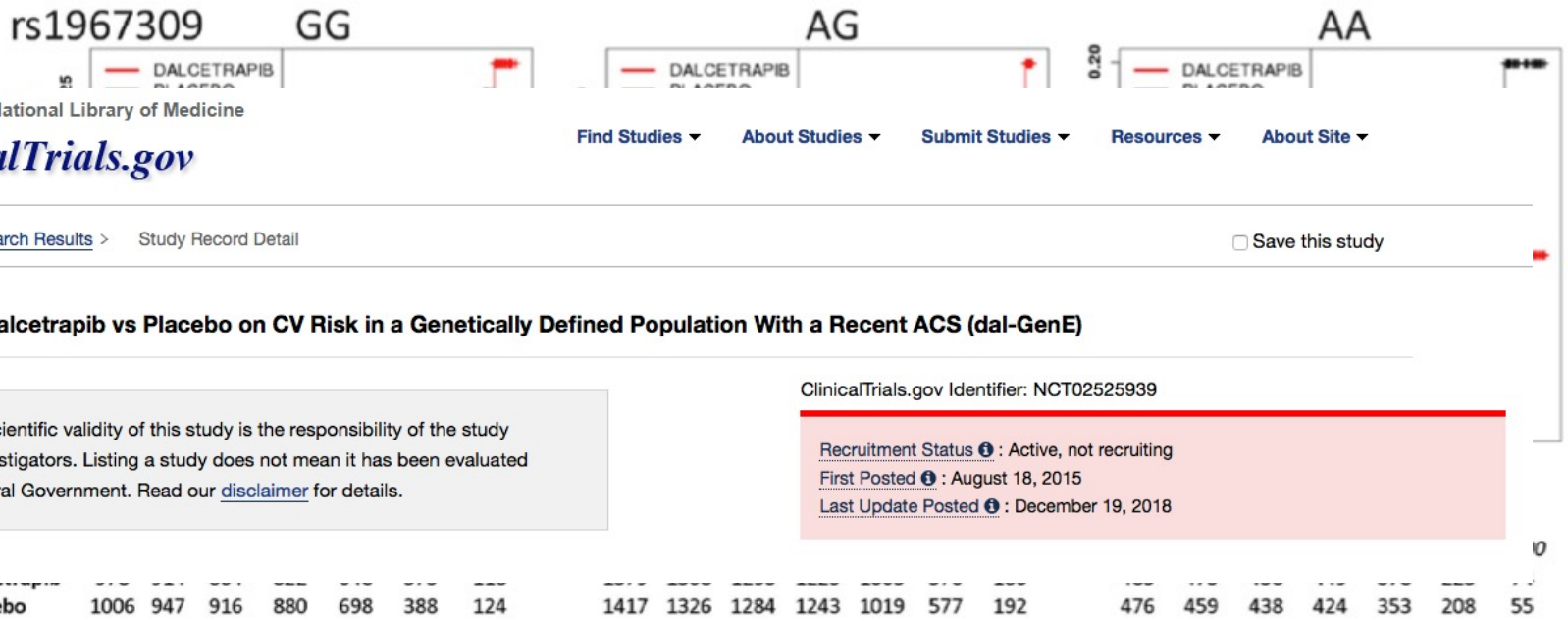
IVUS/angiograhy diagnostic : coronary occlusion : at high heart failure risk



Pharmacogenomics – MI phase 3 clinical trial on GWAS stratification : first personalized cardio metabolism clinical trial

DalCor PHARMACEUTICALS

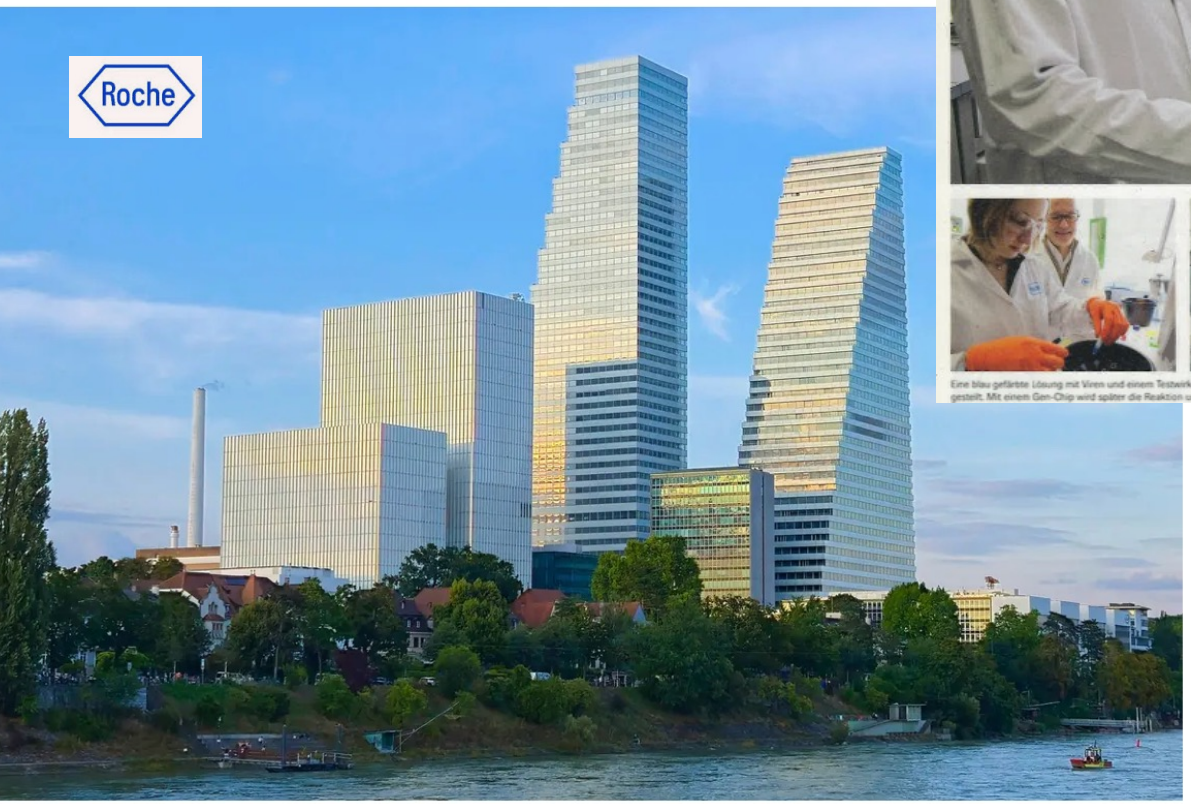
Treatment Effect by *ADCY9* Genotypes in dal-OUTCOMES



Events: Composite of CHD death, resuscitated cardiac arrest, non-fatal myocardial infarction, unstable angina with objective evidence of ischemia, atherothrombotic stroke and unanticipated coronary revascularization

igure. Kaplan–Meier curves of accumulating cardiovascular events in the dalcetrapib and placebo arms broken down according to the enotypes at rs1967309 in the *ADCY9* (adenylate cyclase type 9) gene. CHD indicates coronary heart disease.

Pharmacogenomics – MI phase 3 clinical trial on GWAS stratification : a team work at the core of patient needs



Prof Dr Roger G. Clerc Roche pRED Basel Metabolic Disease

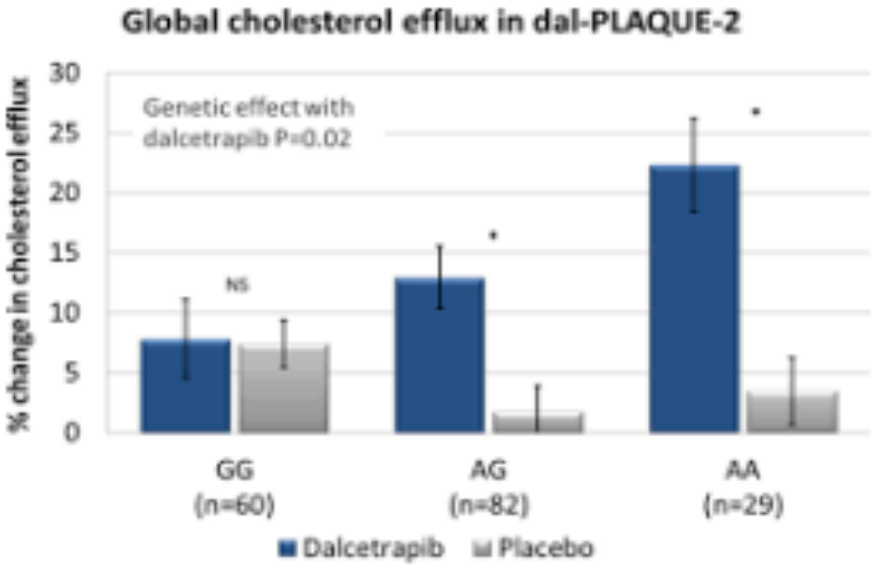
Beneficial effect of increasing reverse cholesterol on a large CVD cohort !?

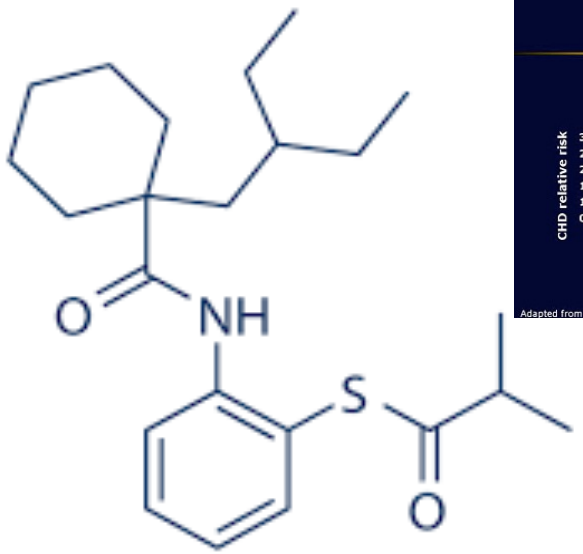
News

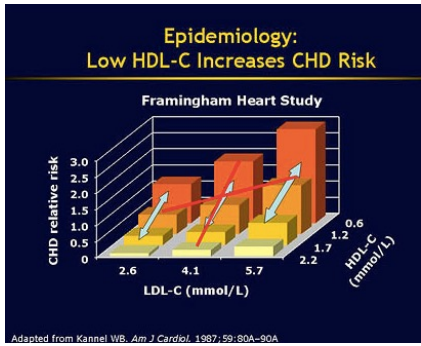
dal-OUTCOMES: Wrestli Inhibitor Failed to Reduc

Michael O'Riordan

CORONARY ARTERY ATHEROSCLEROSIS IS THE SINGLE LARGEST KILLER OF MEN AND WOMEN IN THE DEVELOPED COUNTRIES AROUND THE GLOBE. IT IS THE PRINCIPAL CAUSE OF CORONARY ARTERY DISEASE (CAD), IN WHICH ATHEROSCLEROTIC CHANGES ARE PRESENT WITHIN THE WALLS OF THE CORONARY ARTERIES, WITH HEART FAILURE AND STROKE EVENTS.

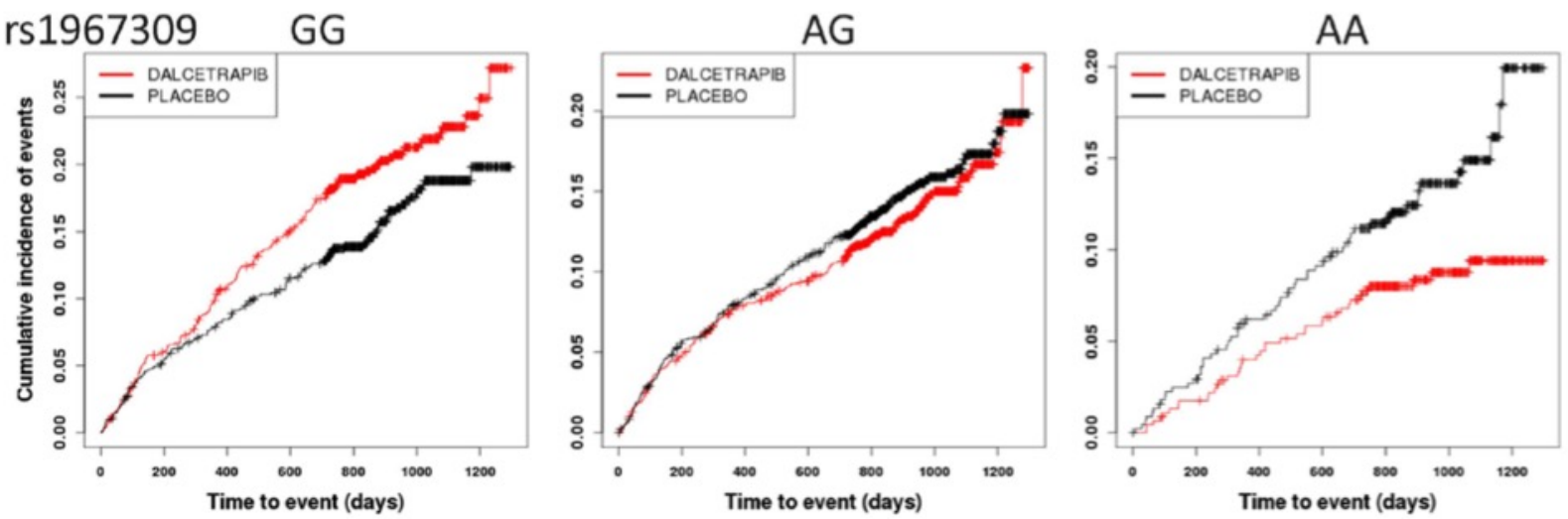






dal – outcome trial : pharmacogenomics_posthoc analysis

Treatment Effect by *ADCY9* Genotypes in dal-OUTCOMES



N at risk/days	*0*	*200*	*400*	*600*	*800*	*1000*	*1200*
Dalcetrapib	978	914	864	822	648	373	118
Placebo	1006	947	916	880	698	388	124

0	*200*	*400*	*600*	*800*	*1000*	*1200*
1379	1308	1255	1225	1003	570	186
1417	1326	1284	1243	1019	577	192

0	*200*	*400*	*600*	*800*	*1000*	*1200*
485	475	458	449	378	223	74
476	459	438	424	353	208	55

Events: Composite of CHD death, resuscitated cardiac arrest, non-fatal myocardial infarction, unstable angina with objective evidence of ischemia, atherothrombotic stroke and unanticipated coronary revascularization

Figure. Kaplan–Meier curves of accumulating cardiovascular events in the dalcetrapib and placebo arms broken down according to the genotypes at rs1967309 in the *ADCY9* (adenylate cyclase type 9) gene. CHD indicates coronary heart disease.

Tardiff et al. (2016) Cir Cardiovasc Genet 116: 340-348

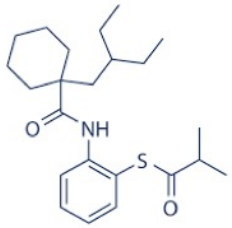
dal – outcome trial : pharmacogenomics_posthoc analysis

CLINICAL PERSPECTIVE

The cholesteryl ester transfer protein inhibitor dalcetrapib effects on cardiovascular outcomes were determined by adenylate cyclase 9 (*ADCY9*) gene polymorphisms in the pharmacogenomic study (n=5749 patients) of dal-OUTCOMES. In patients with genotype AA at rs1967309 in the *ADCY9* gene, there was a 39% reduction in the composite primary cardiovascular end point with dalcetrapib compared with placebo. Supportive results were obtained in the dal-PLAQUE-2 carotid imaging study. In the current study, we determined whether these clinical outcomes and imaging results are associated with concordant changes in reverse cholesterol transport and inflammation. Treatment with dalcetrapib resulted in placebo-adjusted geometric mean percent increases in high-sensitivity C-reactive protein from baseline to end of trial of 18.1% (P=0.0009) and 18.7% (P=0.00001) in participants with GG and AG genotypes, respectively, but change was −1.0% (P=0.89) in those with the protective AA genotype (P=0.02 for treatment arm–genotype interaction). Notably, cholesteryl ester transfer protein inhibitors have been shown to paradoxically increase high-sensitivity C-reactive protein when genotypes are not considered. Although the mean change in cholesterol efflux was similar among study arms in patients with GG genotype (mean: 7.8% and 7.4%), increases were 22.3% and 3.5% with dalcetrapib and placebo for those with AA genotype (P=0.004). There was a significant genetic effect for change in efflux for dalcetrapib (P=0.02), but not with placebo. Genotype-dependent effects on high-sensitivity C-reactive protein and cholesterol efflux are supportive of dalcetrapib benefits on cardiovascular outcomes in patients with the AA genotype at polymorphism rs1967309. A prospective pharmacogenomics-guided clinical trial is being conducted in these responsive patients to allow regulatory review and provide personalized therapy with dalcetrapib.

DalCor PHARMACEUTICALS

ABOUT



CLINICAL TRIAL: DAL-GENE-301

Tardiff et al. (2016) Circ Cardiovasc Genet 116: 340-348
Lindpaintner K et al (2015) Circ Cardiovasc Genet 8: 253-255

THANK YOU.....

DO YOU HAVE ANY QUESTIONS ?

What is the first cause of human death in developed countries ?

A. Cancer
B. Cardiovascular
C. Diabetes
D. Obesity
E. Neurological
F. Don’t know

What is the first cause of human death in developed countries ?

A. Cancer
B. Cardiovascular
C. Diabetes
D. Obesity
E. Neurological
F. Don’t know

How many years on average to discover and develop a new medicine (NME) ?

A. 5 years

B. 10 years

C. 15 years

D. Don’t know

How many years on average to discover and develop a new medicine (NME) ?

A. 5 years

B. 10 years

C. 15 years

D. Don’t know

Pharmacogenomics and pharmacogenetics are essentially :

A. Genome wide linkage study
B. Role of polymorphic genome on drug response
C. Expression quantitative trait analysis eQTL

1: GWAS	A: from bench to bed side and back
2: SNP	B: brings LDL cholesterol back to liver
3: translational research	C: HMGCoA reductase inhibitor (statins)
4: reverse cholesterol	D: genome wide association study
5: most sold medicine sofar	E: single nucleotide polymorphism
6: HTS	F: high throughput SMW cpd screening
7: efficacious D6 metabolizer	G: breast cancer greater survival chances

A. 1D,2C,3E,4B,5A,6F,7G

B. 1D,2C,3E,4A,5B,6F,7G

C. 1G,2D,3A,4E,5B,6F,7C

D. 1D,2E,3A,4B,5C,6F,7G

WHICH SERIES IS CORRECT ?