From rare to common disease, from genetics to therapy

Personalized lipid-lowering therapy?

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umcg

No disclosures

Worlwide impact of atherosclerosis

the pathology underlying cardiovascular disease

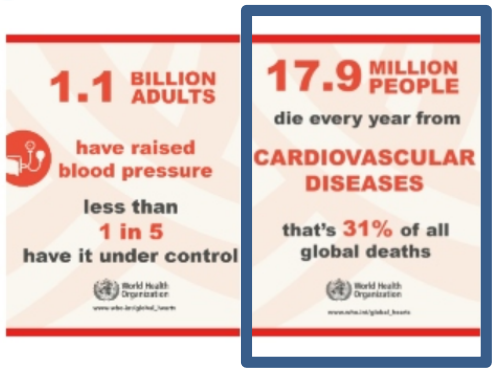
World Health Organization

Health topics | Countries | News | Emergencies | About us

Cardiovascular disease

- Cardiovascular disease
- Strategic priorities
- Global Hearts Initiative
- Research and global partnerships
- Regional activities
- Multisector partnerships
- WRIGHT project
- Publications

On World Heart Day WHO calls for accelerated action to prevent the world's leading global killer



Cardiovascular diseases (CVDs) take the lives of 17.9 million people every year, 31% of all global deaths. Triggering these diseases are tobacco smoking, unhealthy diet, physical inactivity and the harmful use of alcohol. These in turn show up in people as raised blood pressure, elevated blood glucose and overweight and obesity. Through the Global Hearts Initiative, WHO is supporting governments to scale-up efforts on CVD prevention and control through three technical packages: MPOWER for tobacco control, SHAKE for salt reduction and HEARTS for strengthening CVD management in primary health care. Launched in September 2016, the initiative has been rolled out in several countries, where health workers are being trained to better deliver tested and affordable measures to protect people from CVDs and help them recover following a heart attack or stroke. A new global initiative - Resolve to Save Lives - will give renewed impetus to these efforts.

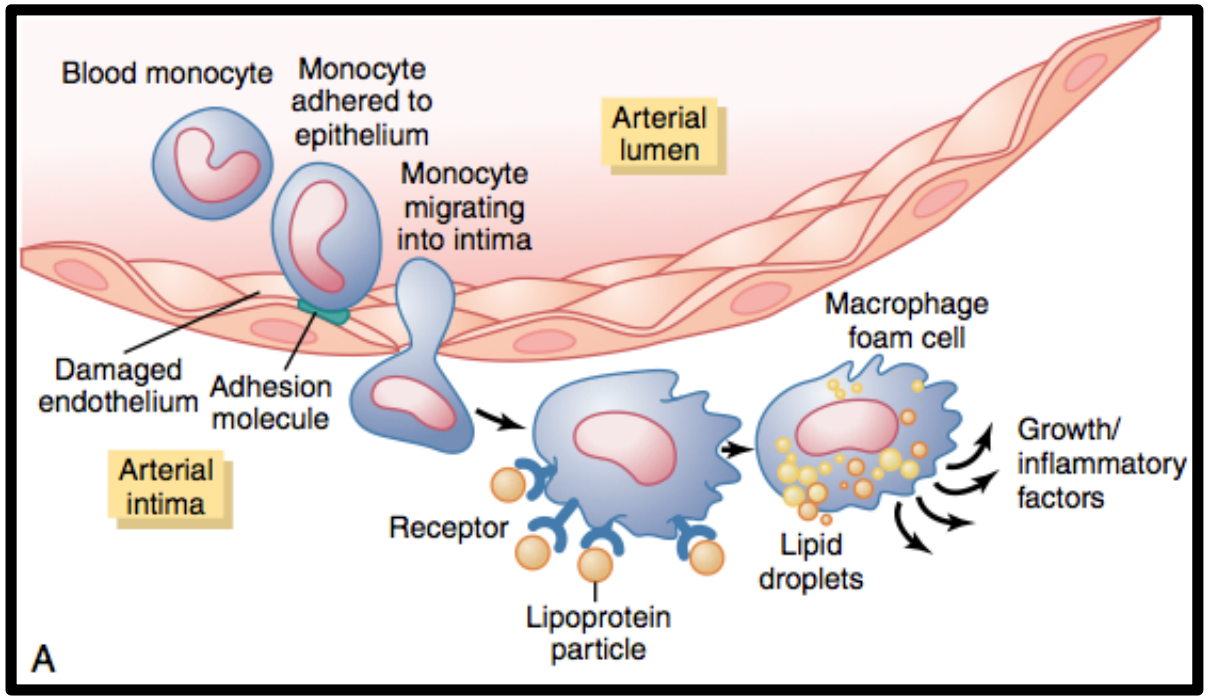
Sept 29, 2018

http://www.who.int/cardiovascular_diseases/en/

Etiology of atherosclerosis

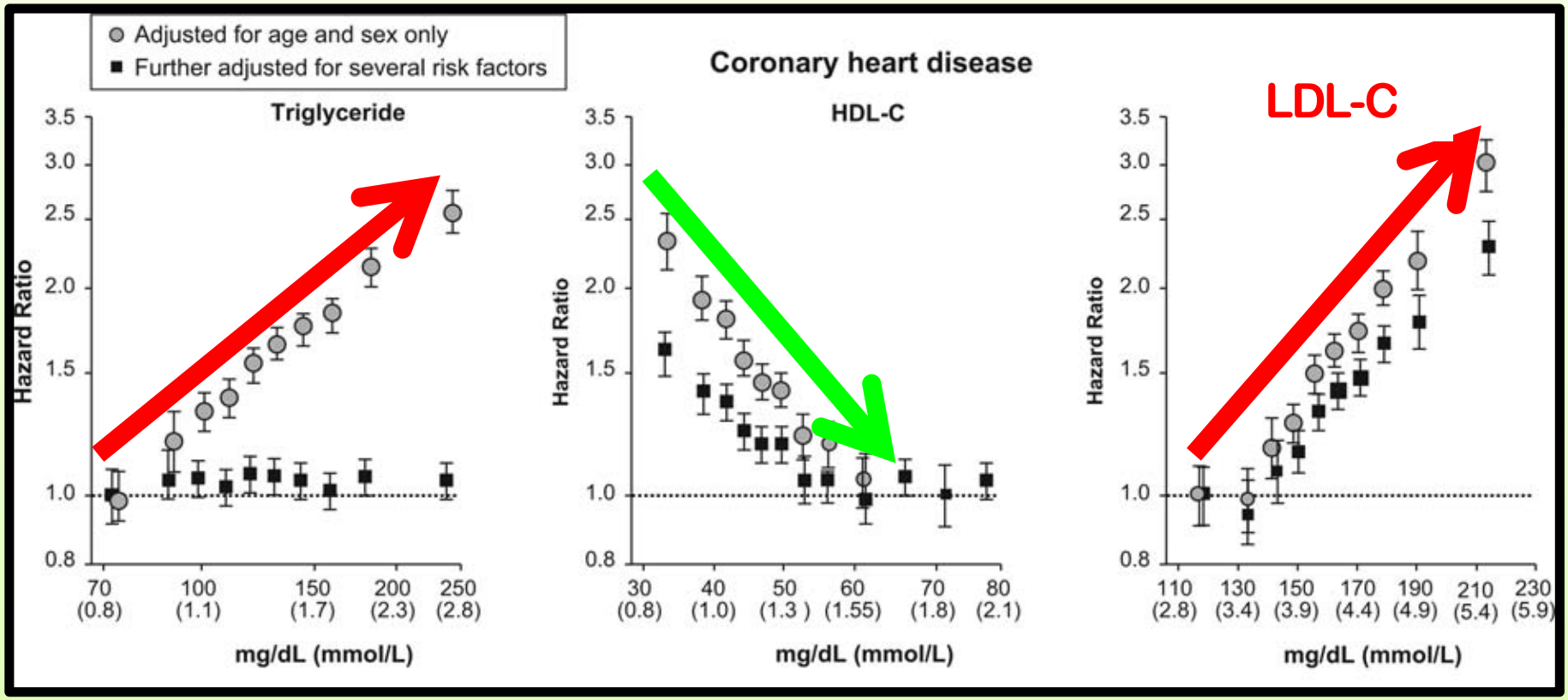
'A lipid driven inflammatory disorder'

Blood lipids ↔ Immunity



Hall and Guyton; textbook of Medical Physiology

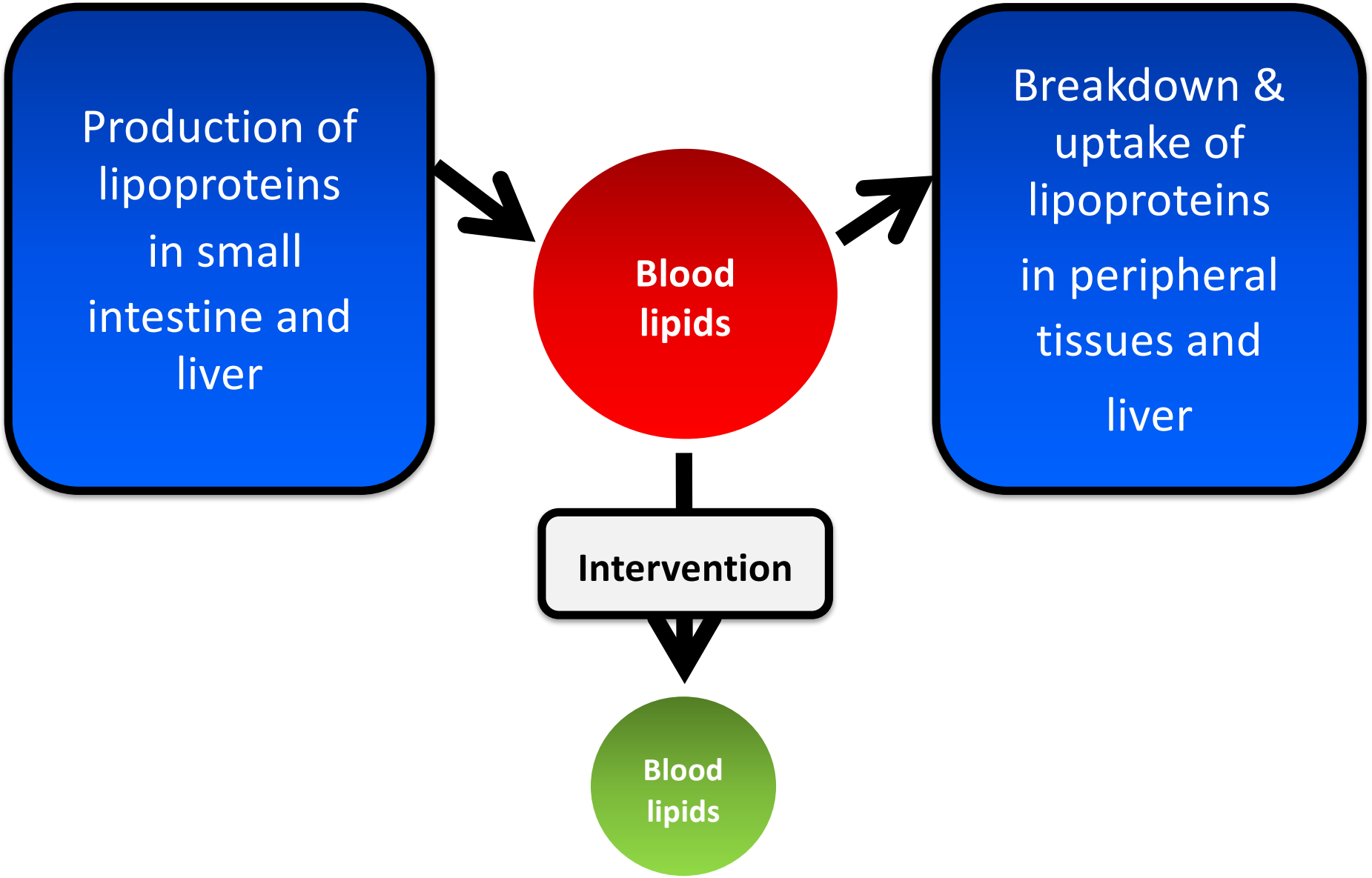
Coronary heart disease risk and plasma lipid levels



General population. No prior CVD; 68 studies; n>300.000

JAMA 2009;302:1993–2000

Regulation of blood lipid levels



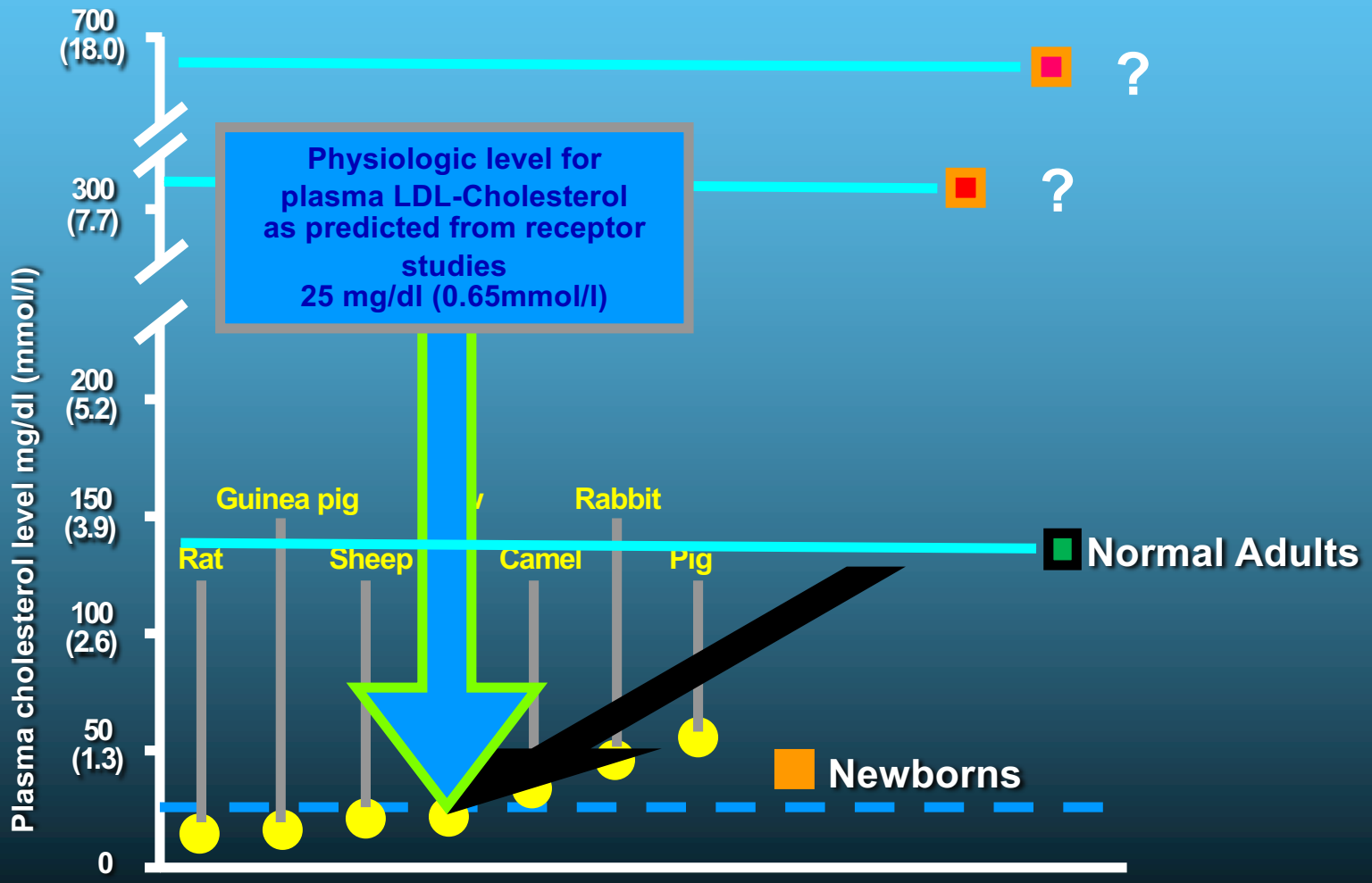
Concept: extreme human genetics to find targets for pharmaceutical intervention

'A naturally occurring genetic variant, which causes a clinically significant phenotype indicates that the mutated gene product - and thus the wild type gene product - must be relevant to physiology'

Kuivenhoven JA & Hegele RA; BBA. 2014

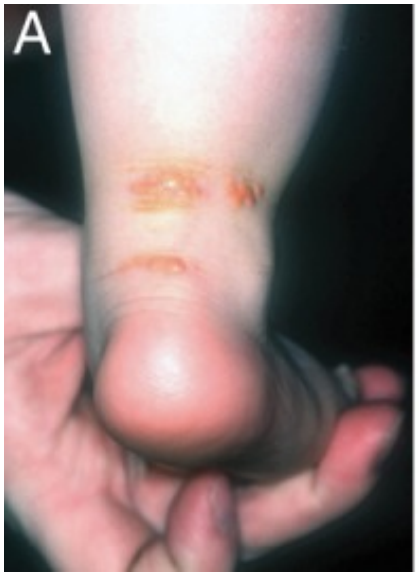
PMID: 24798233

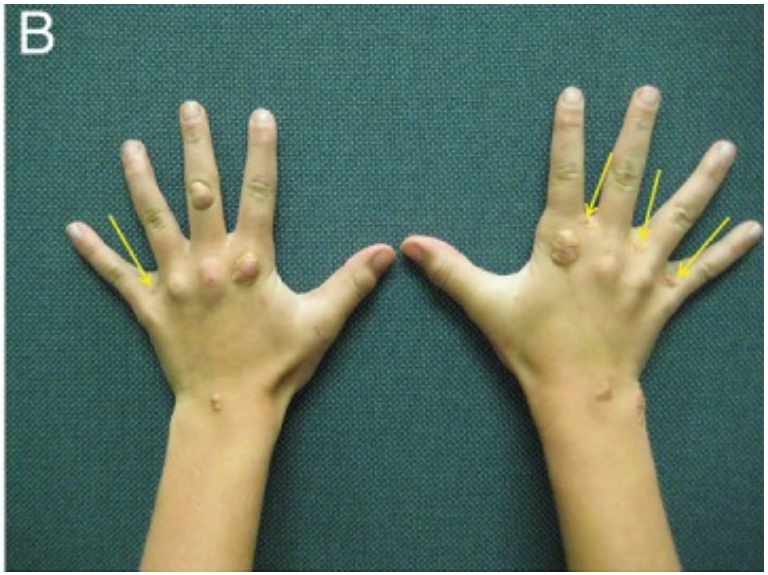
Extreme LDL cholesterol

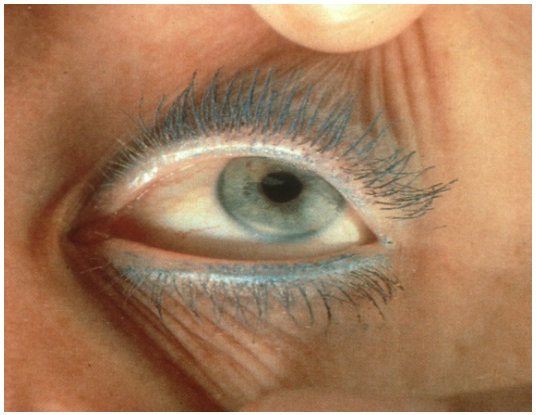


Familial hypercholesterolemia (FH)

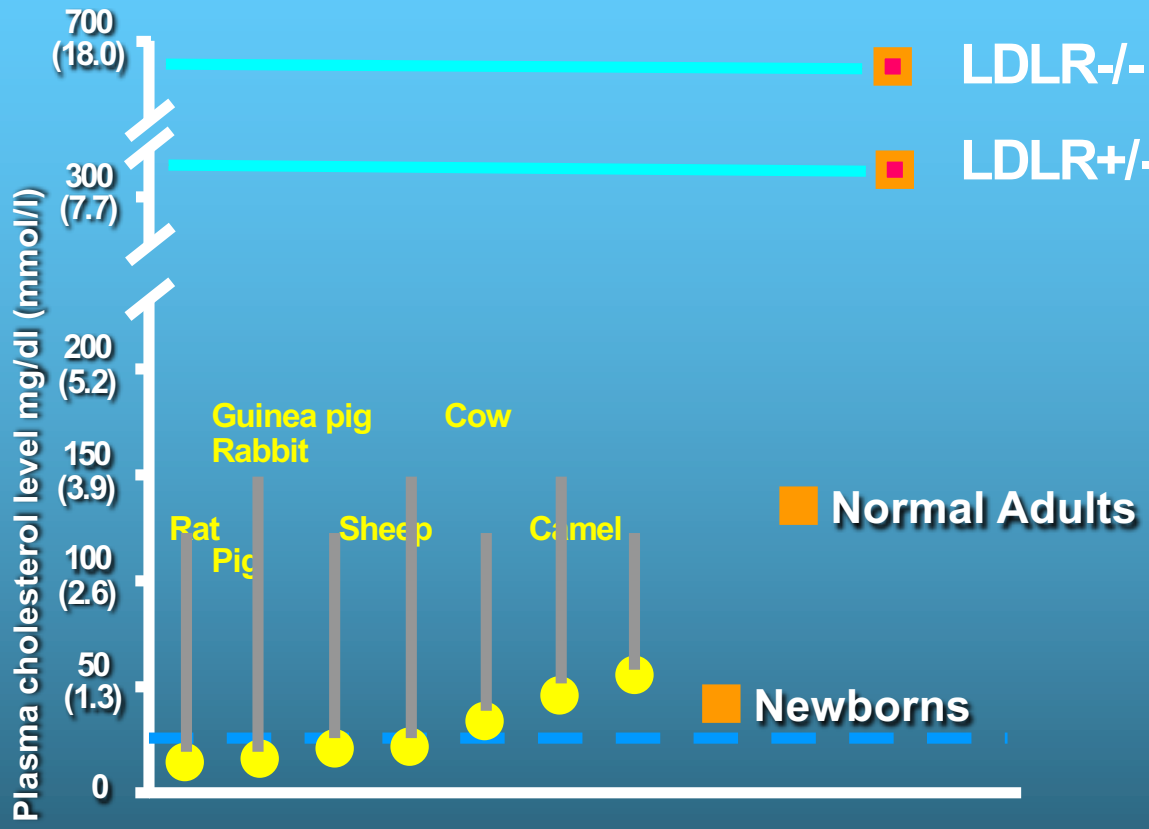
Frequency 1:250

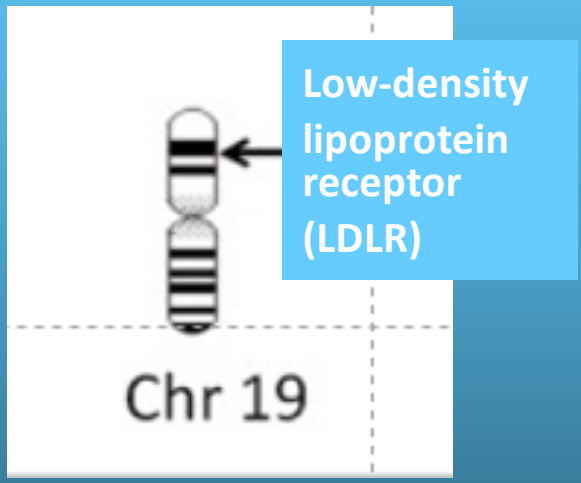






Mutations in LDLR causing FH

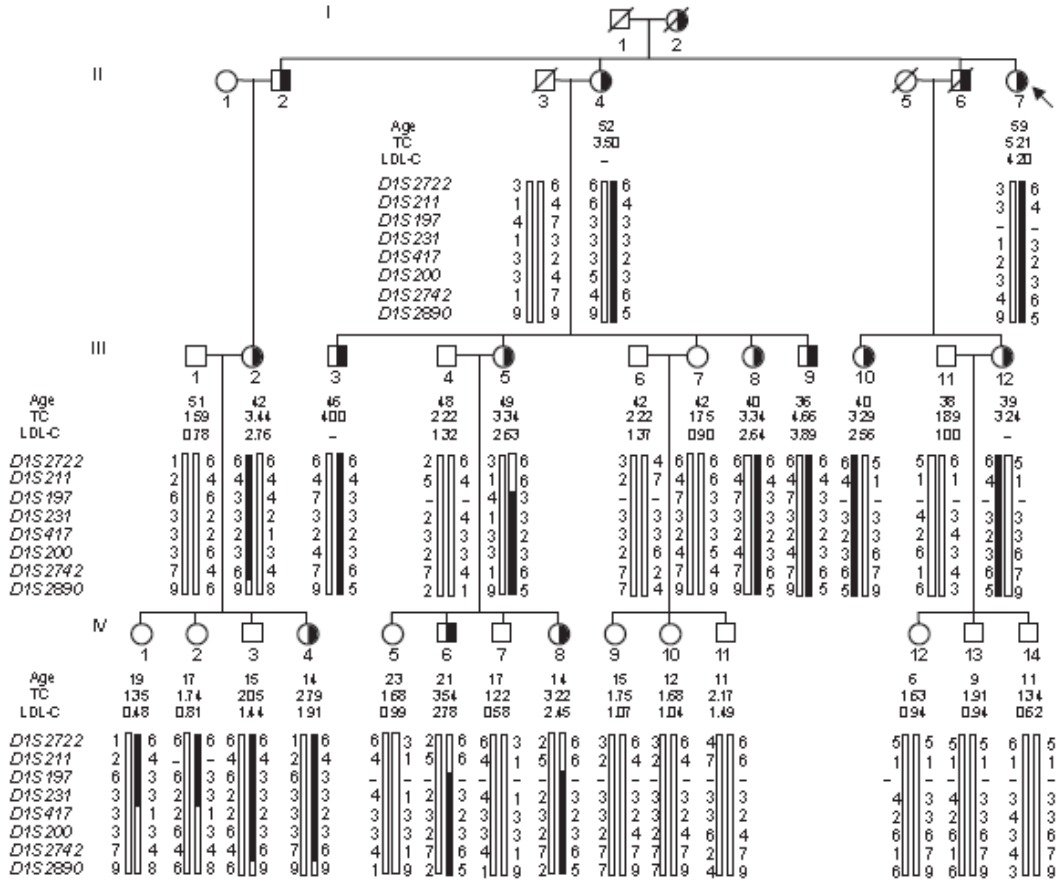




Nobel prize in Phsiology or Medicine 1985 (Goldstein & Brown)

Their discoveries concerning the regulation of cholesterol metabolism provided the basis to the development of statins.

A single family with FH of unknown etiology



Abifadel M et al. NatGen 2003

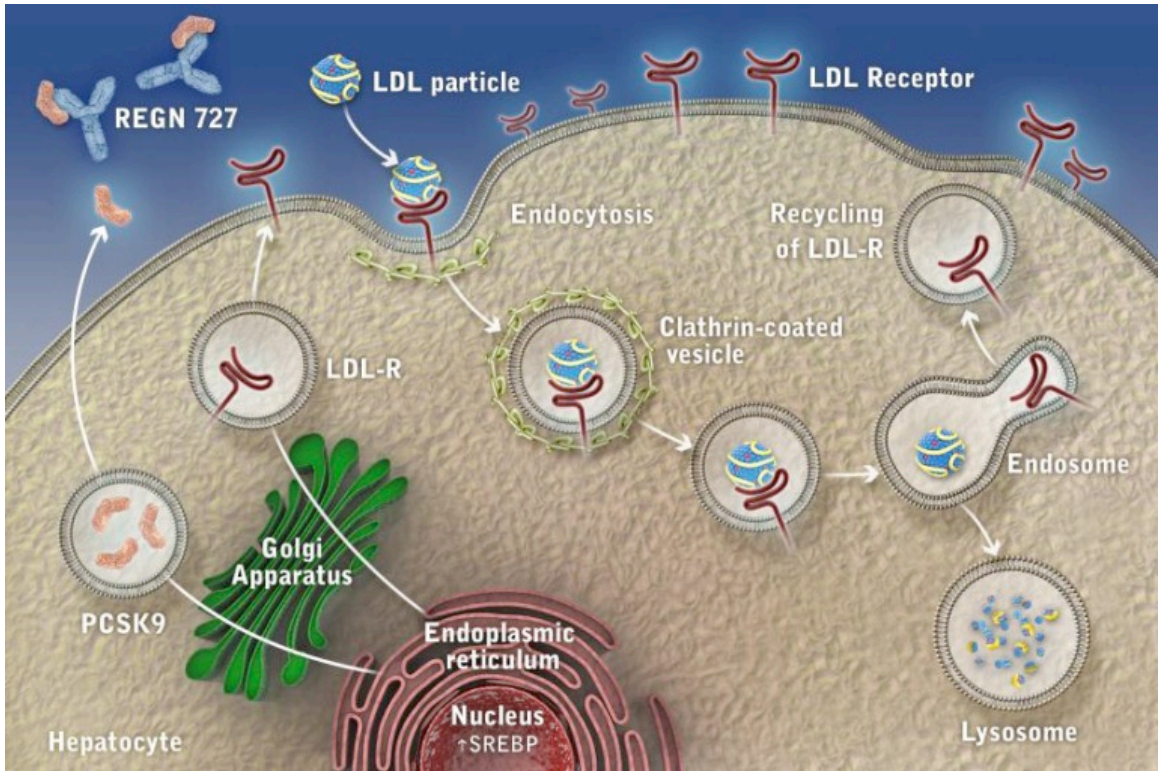
Identification of PCSK9 as a novel LDL candidate gene in a single family.

From rare variants to treatment of common disease

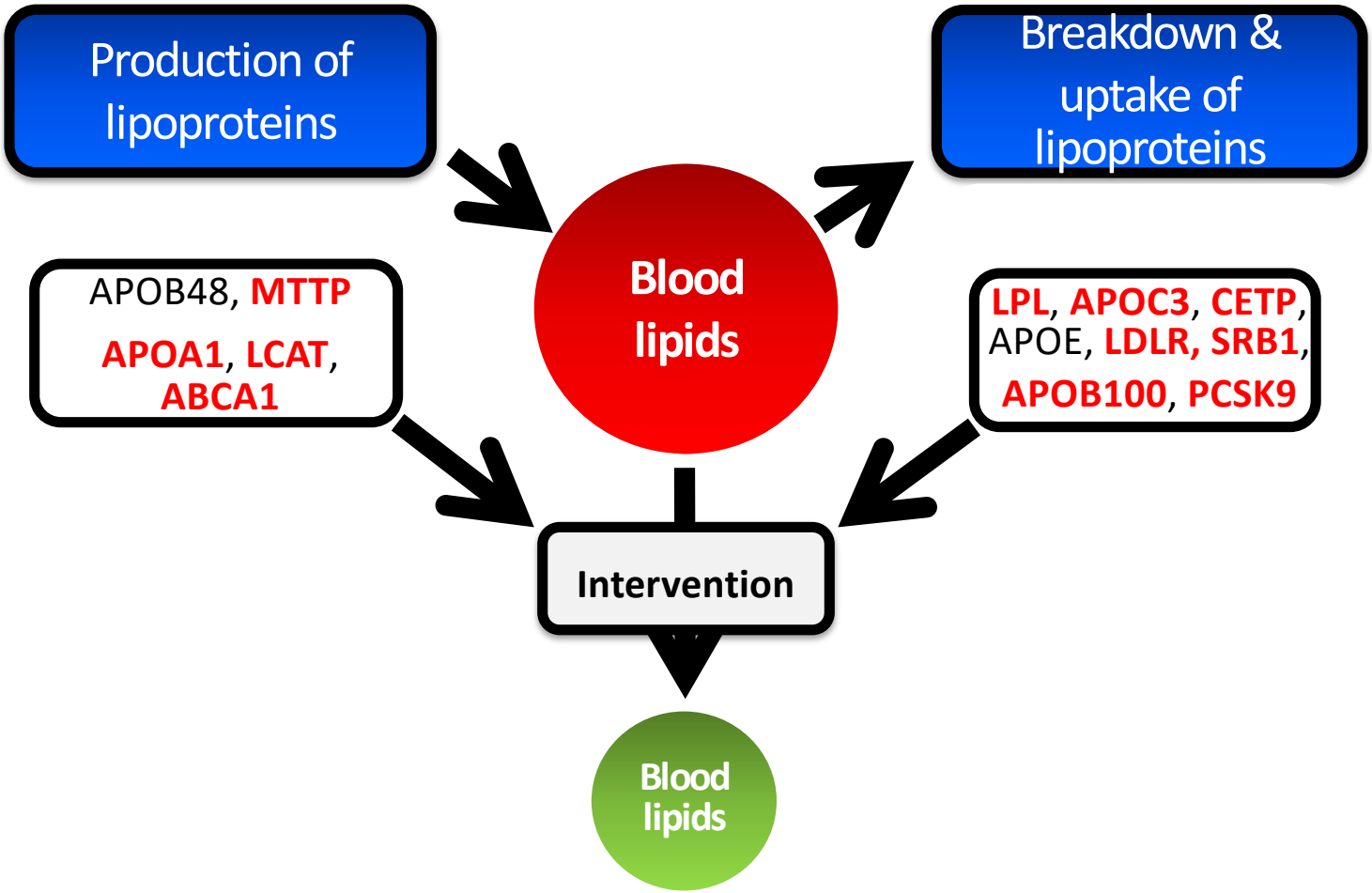
- *PCSK9* mutations: 0.2% of patients with FH
- 2015: EMEA/FDA approval to use PCK9i to lower LDLc

Mechanism:

promotion reuse of LDLR

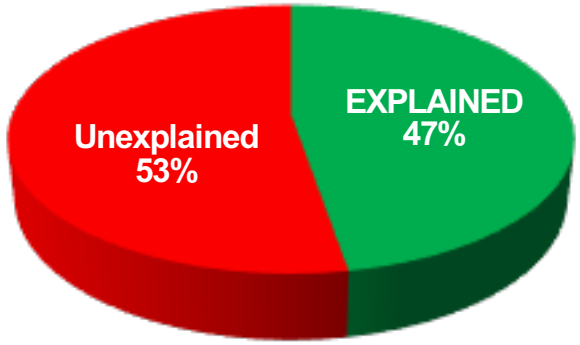


Monogenic origins of human dyslipidemia are drug targets

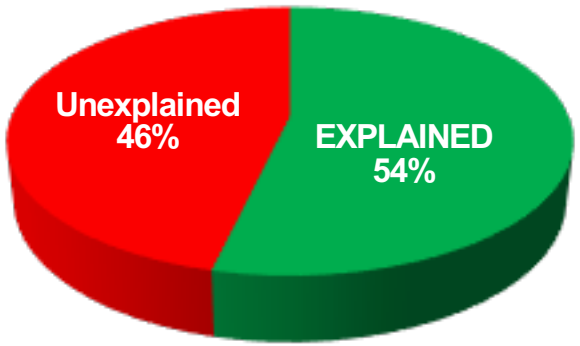


Monogenic, polygenic and unexplained FH

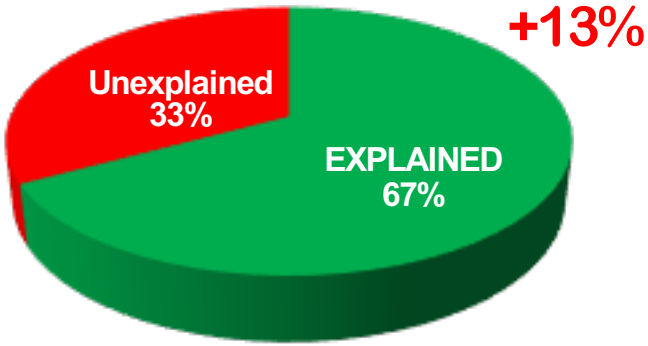
LDLc > 5.0 mmol/l
Monogenic



LDLc > 5.0 mmol/l
Monogenic + CNV



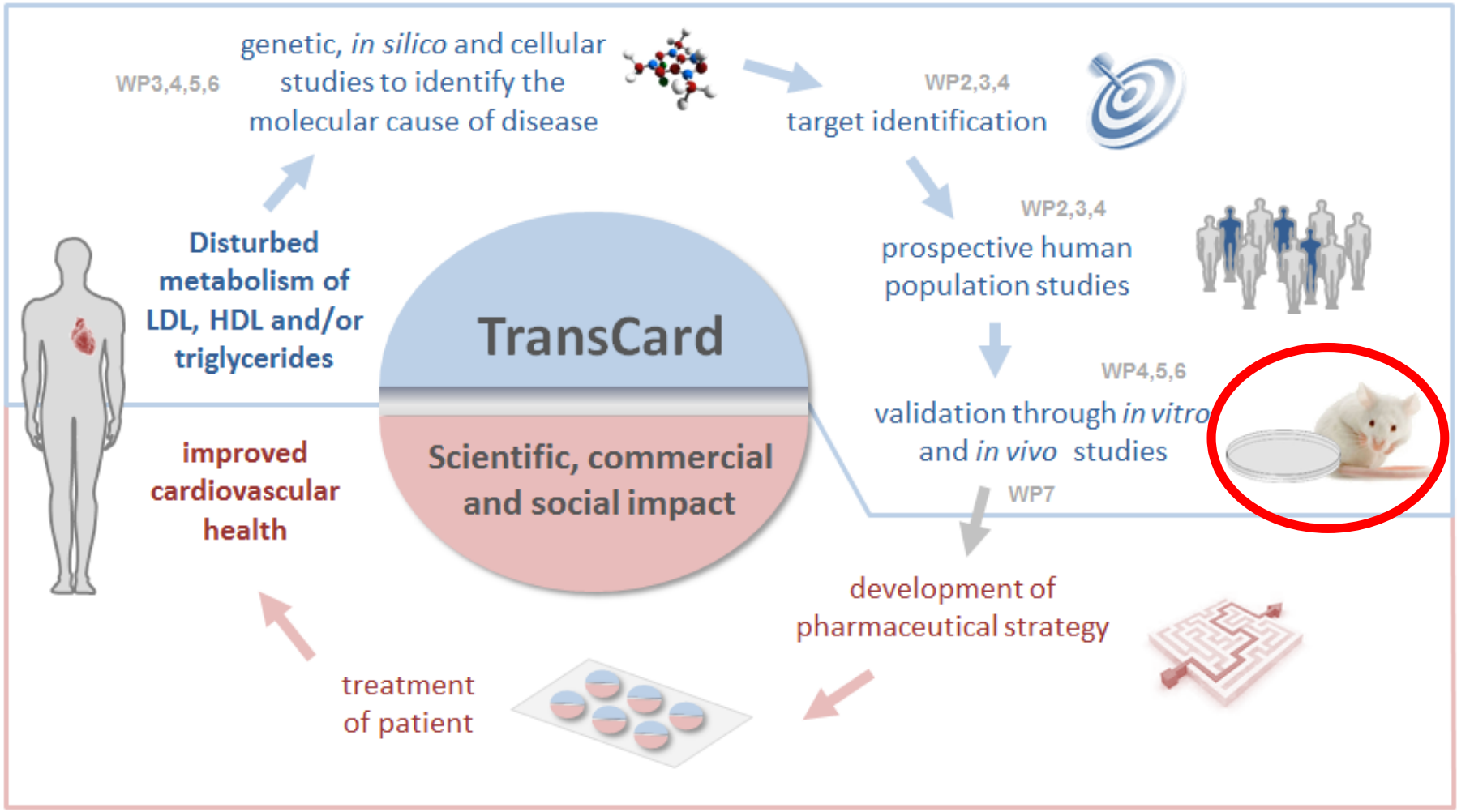
LDLc > 5.0 mmol/l
Monogenic, CNV + Polygenic



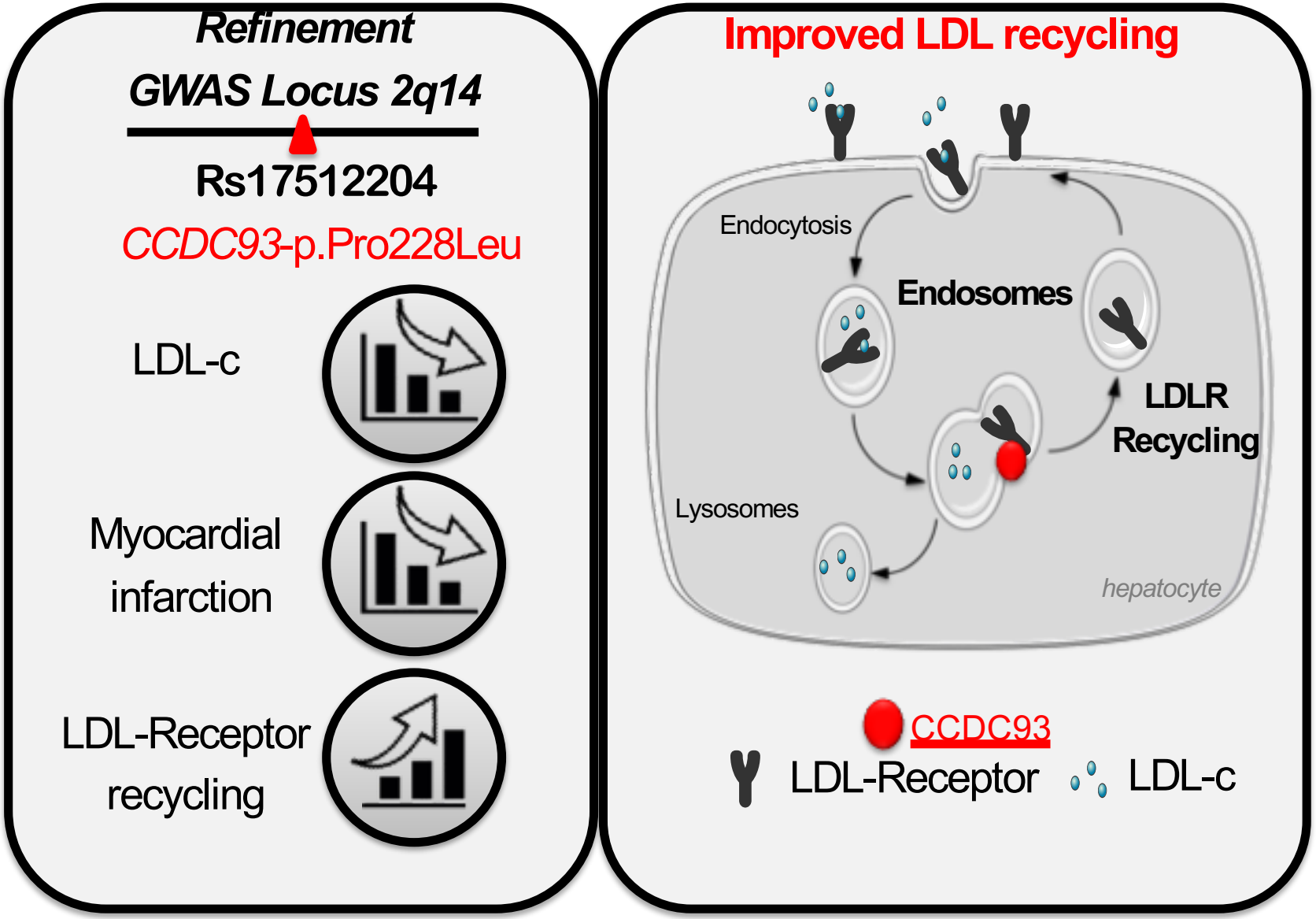
LDLc > 8.0 mmol/l
Monogenic

Wang J et al ATVB 2016

Finding additional lipid pathways



Animal data & human genetics (GWAS)



Rimbert et al. Unpublished data

Personalized lipid-lowering therapy?

Facing the facts

Treated when clinical events have occured

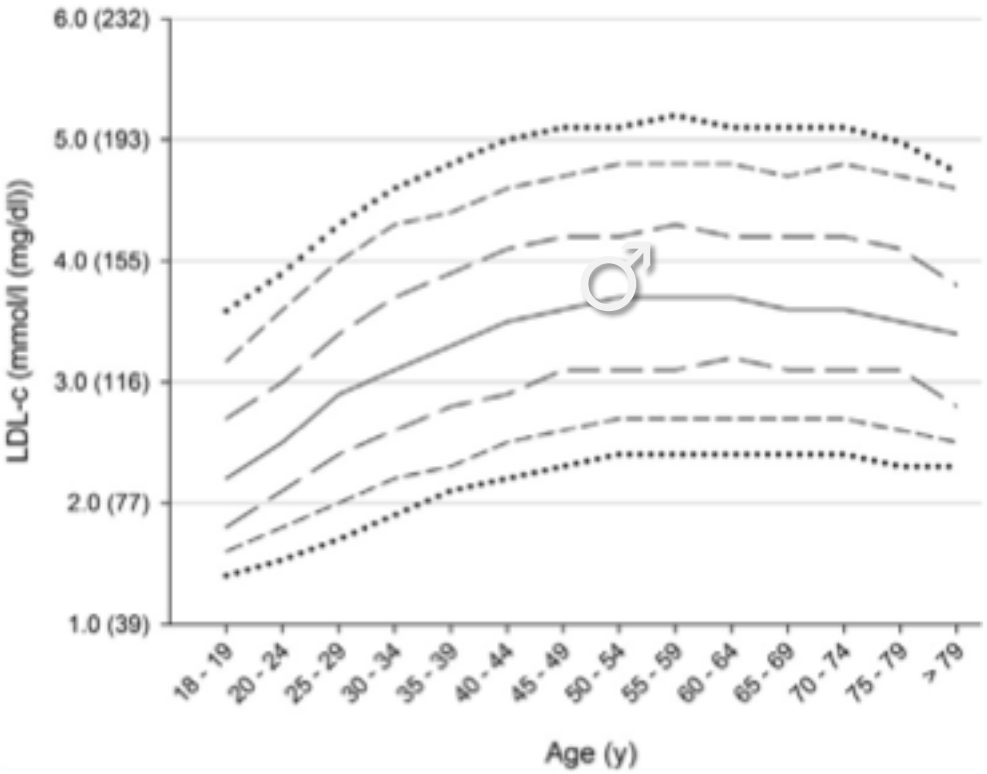
at 60 euro/yr (statins)

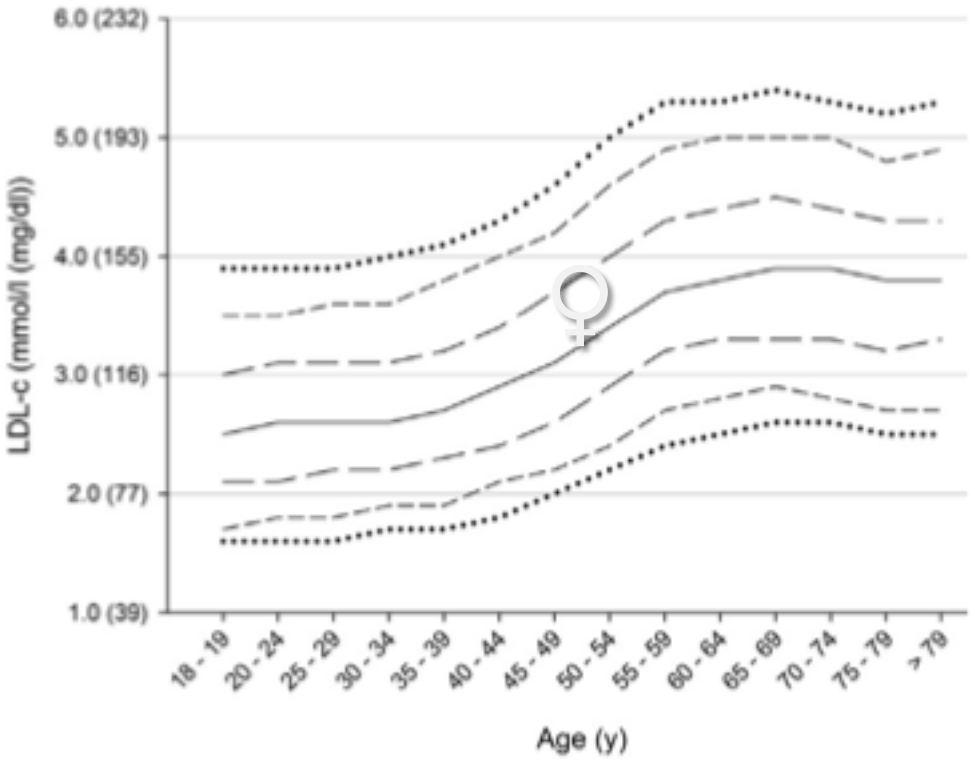
umcg

Personalized lipid-lowering therapy?

Facing the facts: LDL cholesterol, age and gender

♂ ≠ ♀





LifeLines

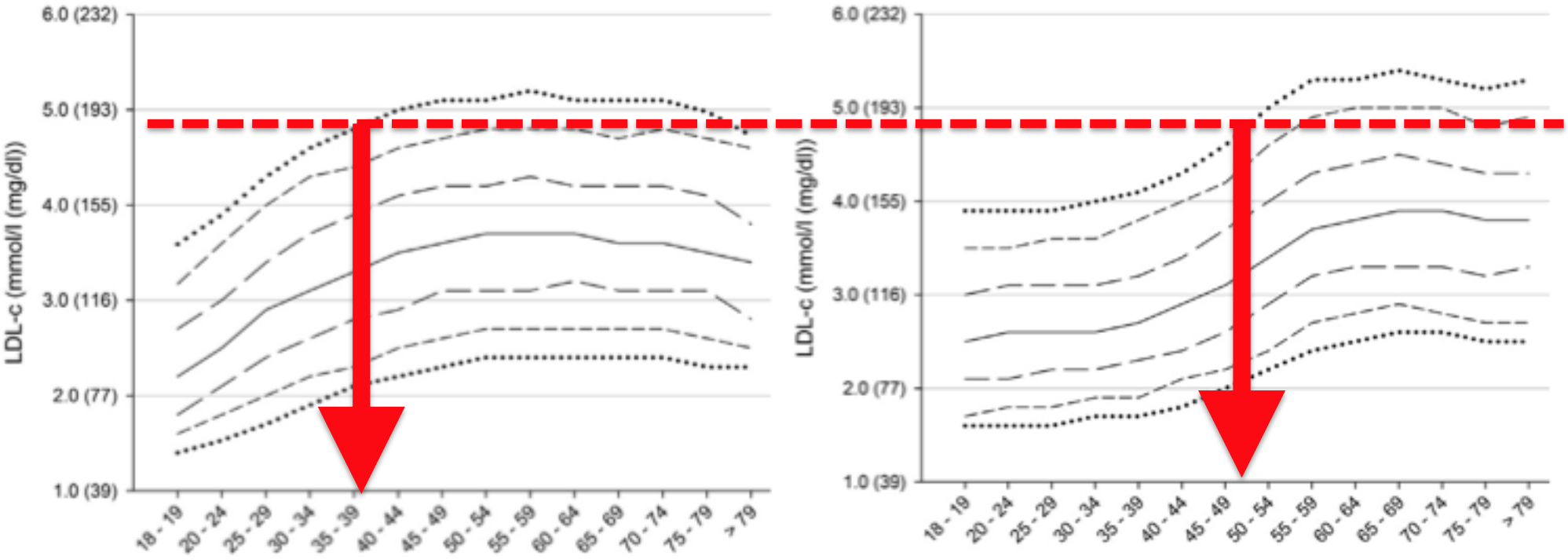
Balder et al. JClinLip 2017

Personalized lipid-lowering therapy?

Facing the facts: use of fixed LDLc cutoff

Intervention criterion:

4.9 mmol/L (200mg/dl)



35-40 yo

45-50 yo

LifeLines

Balder et al. JClinLip 2017

Personalized lipid-lowering therapy?

One treatment for all = general practice

Prediction of 10 year CVD risk (Framingham/Procam)

High / Medium / Low risk

↓

Lifestyle modification &

Pharmaceutical intervention when LDL-c > 4.9mmol/l (200mg/dl)

↓

Statins - first choice (inhibition of *de novo* cholesterol synthesis)

Add on therapy (Colesevalam / Ezetimibe) (cholesterol absorption inhibition)

Personalized lipid-lowering therapy?

Special treatment driven by costs and orphan annotation

PCSK9i at 17k dollar/yr (US) or 7k euro/yr (NL) for

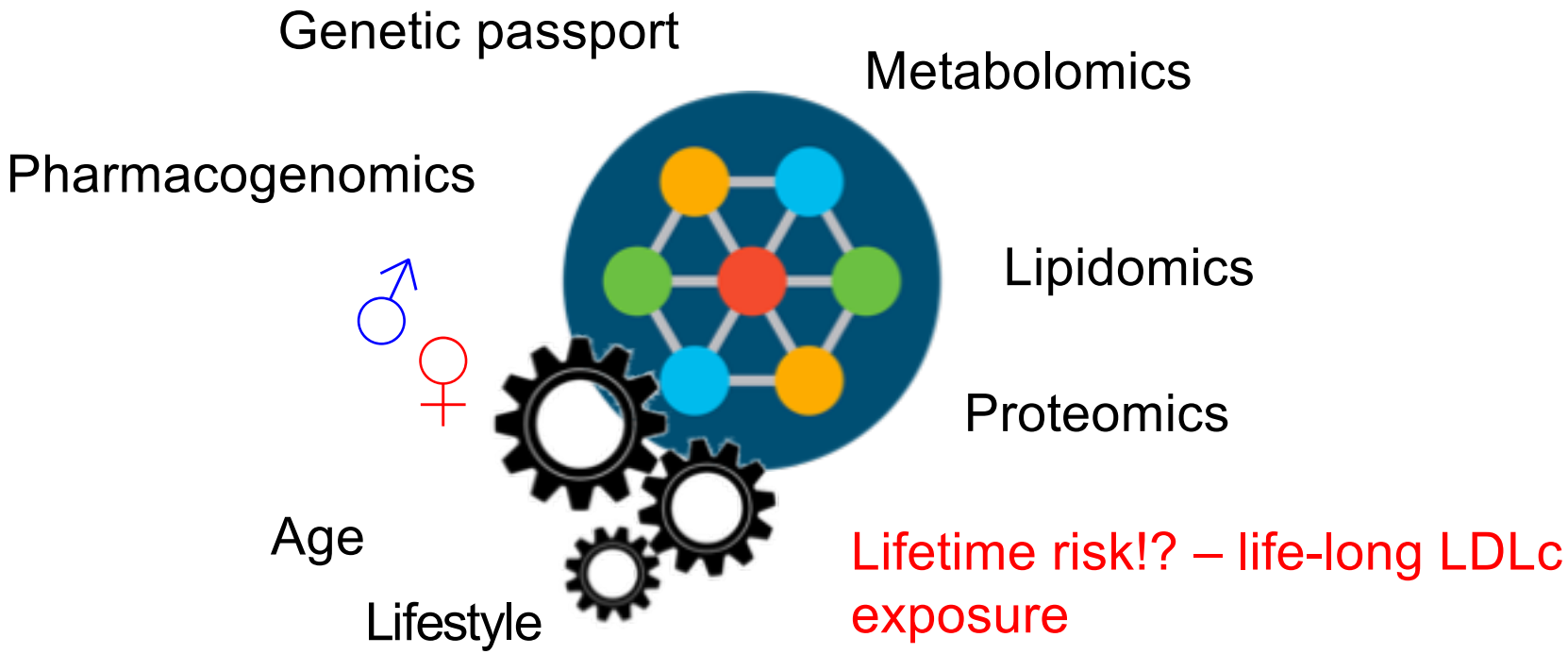
- homozygous FH
- high-risk patients not reaching LDLc targets
- statin-intolerance

Treating severe (homozygous) FH:

- Lomitapide (MTTPi): 500-600k Euro/yr.
- Mipomersen (antisense apoB): 167k/yr

Personalized lipid-lowering therapy?

Perspective



Data integration to improve care?

Data integration to find new targets

Focus on groups of individuals with **similar 'fingerprints'** **to help finding new pathways that regulate plasma lipid levels**

Acknowledgements

UMCG Groningen

Antoine Rimbert – geneticst – PD

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Peter Lansberg – physician/lipidologist

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Dr. Hinda Daggag – Abu Dhabi, UAE

Dr. Jeanine Roeters van Lennep – Rotterdam, NL

Prof. Arnold von Eckardstein, Zurich, CH

Funding bodies

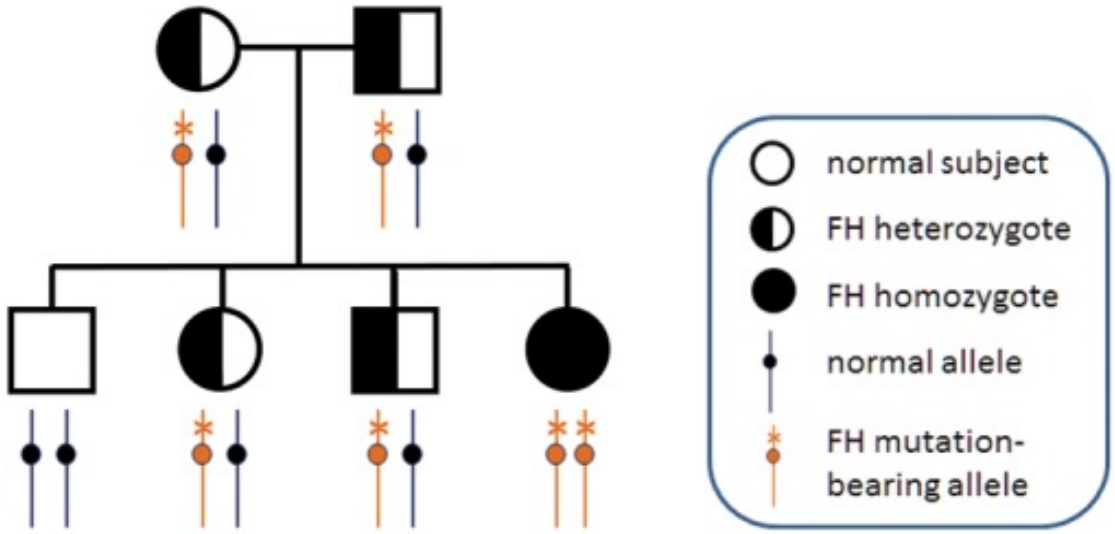
CVON
CardioVascular Onderzoek Nederland

SEVENTH FRAMEWORK PROGRAMME

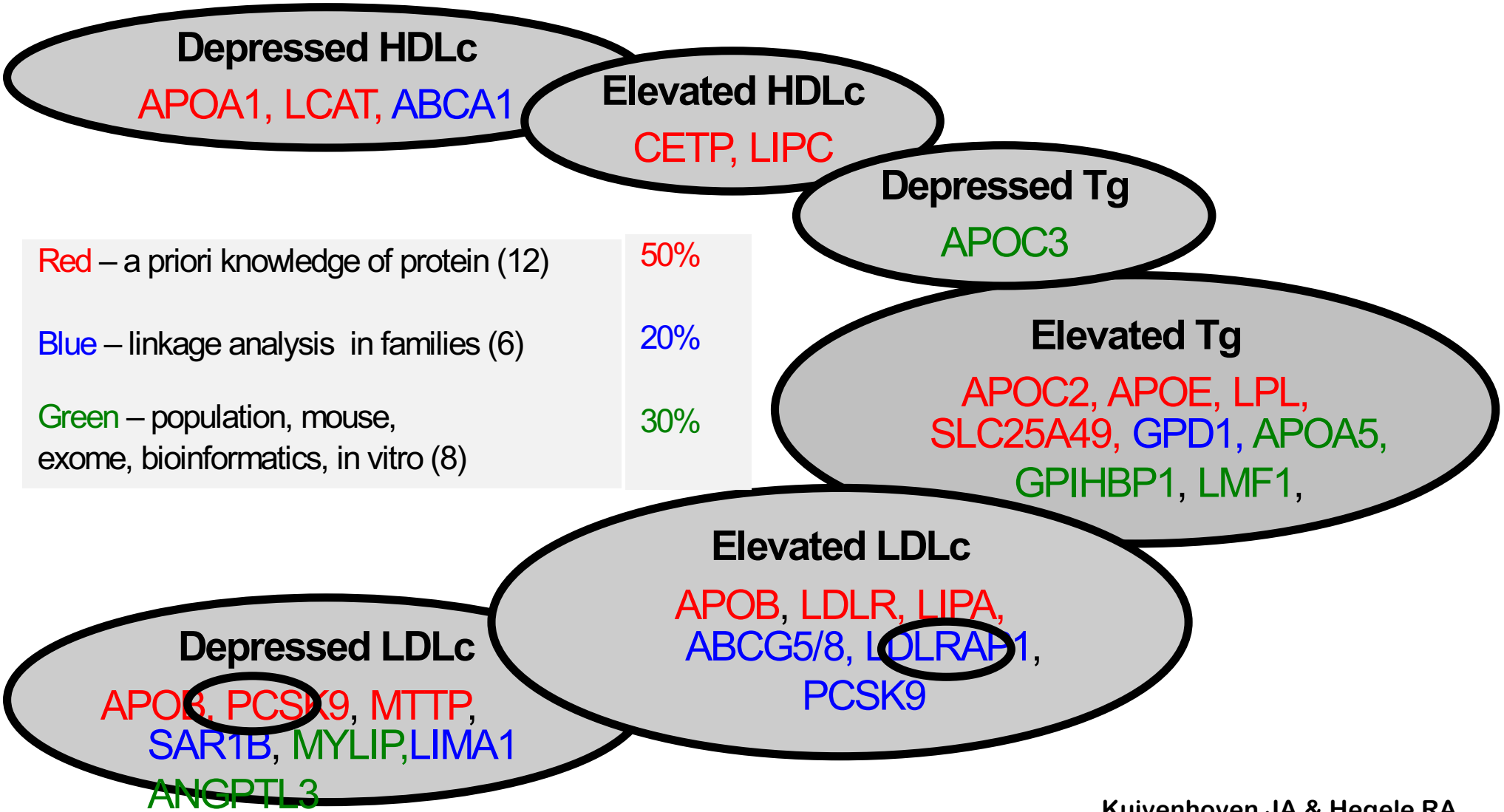
funded by the dutch heart foundation

Hartstichting

Pattern of inheritance of FH



Human monogenic lipid disorders



Zhang YY et al. Science 2018. PMID: 29880681

Kuivenhoven JA & Hegele RA. BBA. Review. PMID: 24798233

NatGen 2003

Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia

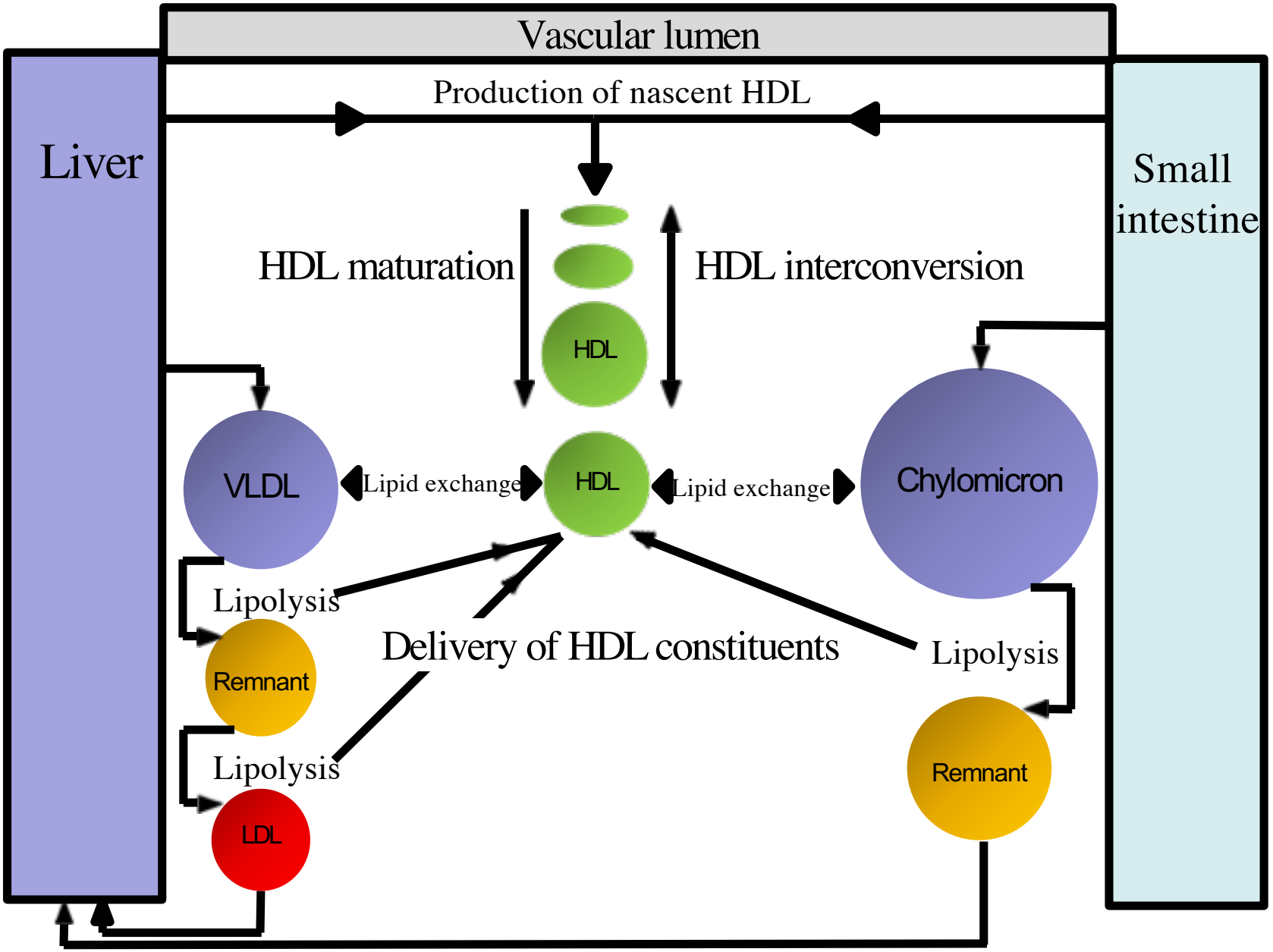
Marianne Abifadel[1,2], Mathilde Varret[1], Jean-Pierre Rabès[1,3], Delphine Allard[1], Khadija Ouguerram[4], Martine Devillers[1], Corinne Cruaud[5], Suzanne Benjannet[6], Louise Wickham[6], Danièle Erlich[1], Aurélie Derré[1], Ludovic Villéger[1], Michel Farnier[7], Isabel Beucler[8], Eric Bruckert[9], Jean Chambaz[10], Bernard Chanu[11], Jean-Michel Lecerf[12], Gerald Luc[12], Philippe Moulin[13], Jean Weissenbach[5], Annick Prat[6], Michel Krempf[4], Claudine Junien[1,3], Nabil G Seidah[6] & Catherine Boileau[1,3]

Autosomal dominant hypercholesterolemia (ADH; OMIM144400), a risk factor for coronary heart disease, is characterized by an increase in low-density lipoprotein cholesterol levels that is associated with mutations in the genes ***LDLR*** (encoding low-density lipoprotein receptor) or ***APOB*** (encoding apolipoprotein B). We mapped a third locus associated with ADH, ***HCHOLA3*** at 1p32, and now report two mutations in the gene ***PCSK9*** (encoding proprotein convertase subtilisin/kexin type 9) that cause ADH. ***PCSK9*** encodes NARC-1 (neural apoptosis regulated convertase), a newly identified human subtilase that is highly expressed in the liver and contributes to cholesterol homeostasis.

To identify the third locus associated with ADH (called *HCHOLA3* or *FH3*), which we previously mapped[1] to 1p34.1–p32 (OMIM 603776) and was confirmed in a large Utah kindred[2], we carried out positional cloning using the family in whom linkage was originally identified

Abifadel M et al. NatGen 2003

Human lipoprotein metabolism



EAS Consensus paper - Eur Heart Journal 2011

Plasma Lipid Management to treat CVD
Perspective

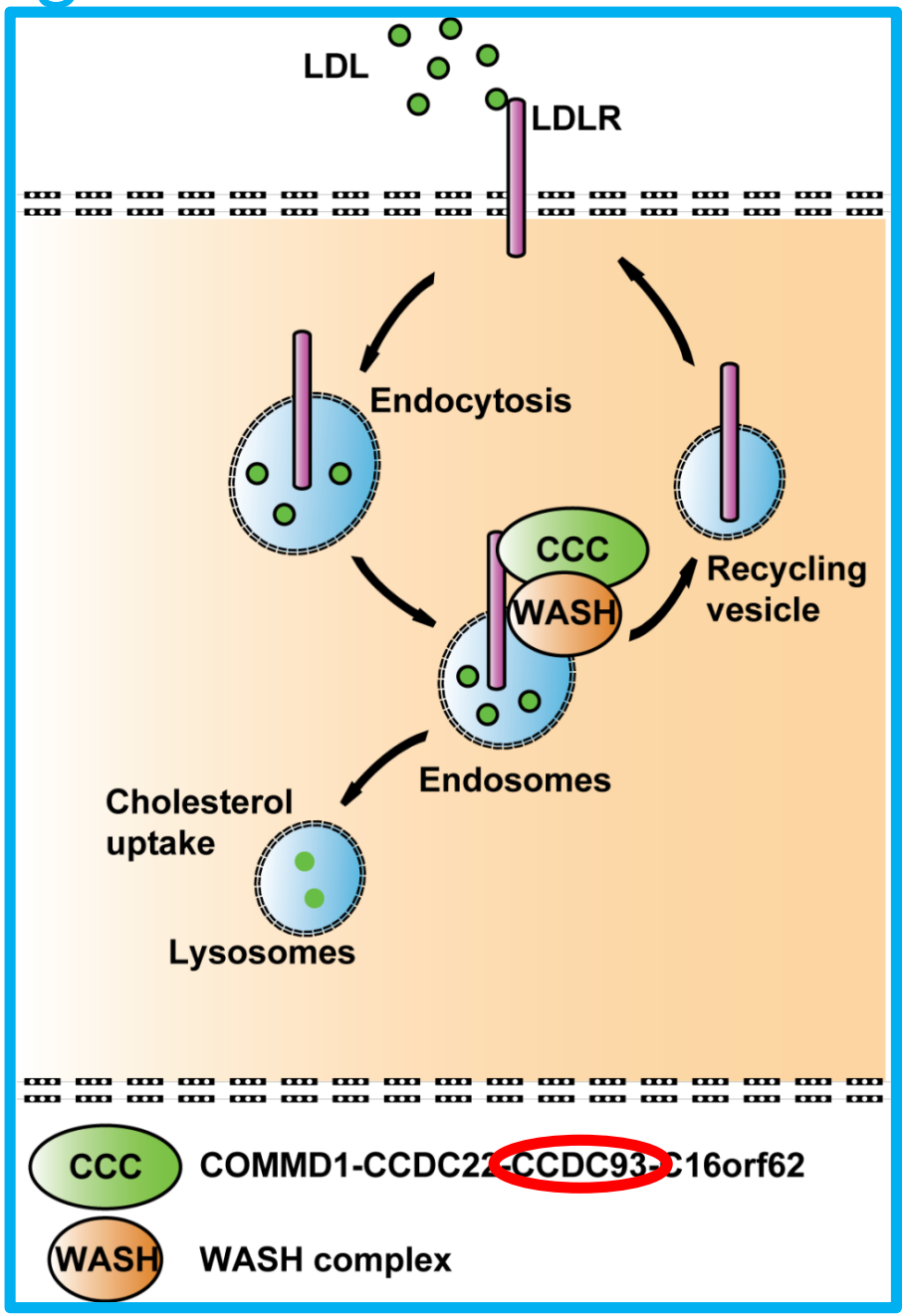
- Age- and gender specific criteria? = not evidence based
- Selection based genetic make-up?
- Pharmacogenetics?

Increased understanding of LDL receptor trafficking

COMMD1 crucial component of a protein complex regulating the plasma LDL cholesterol levels in humans and mammals

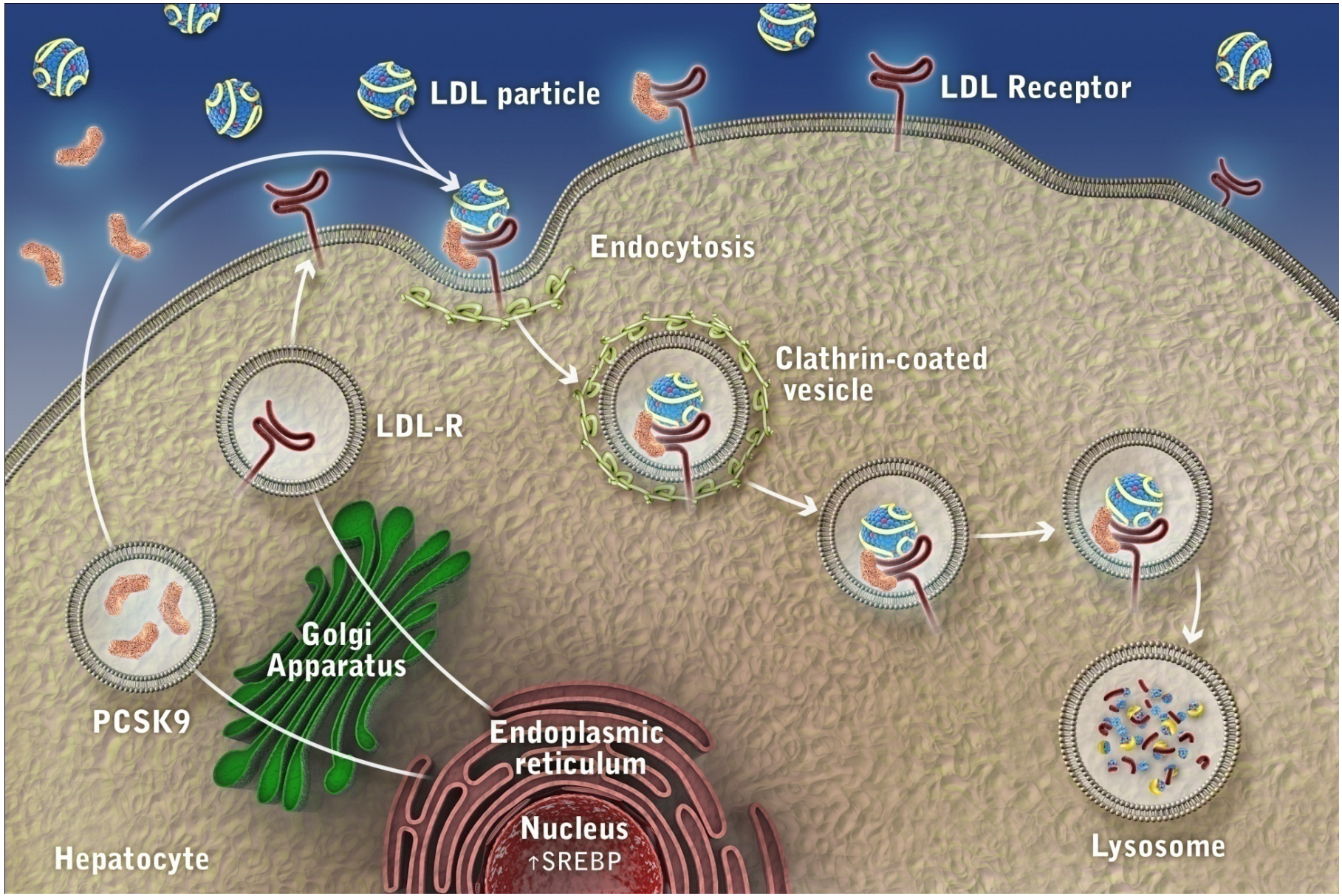
CCC-complex mediates the endosomal sorting of LDLR

WASH complex involved in LDLR sorting



Courtesy Bart vd Sluis

The Role of PCSK9 in the Regulation of LDL Receptor Expression

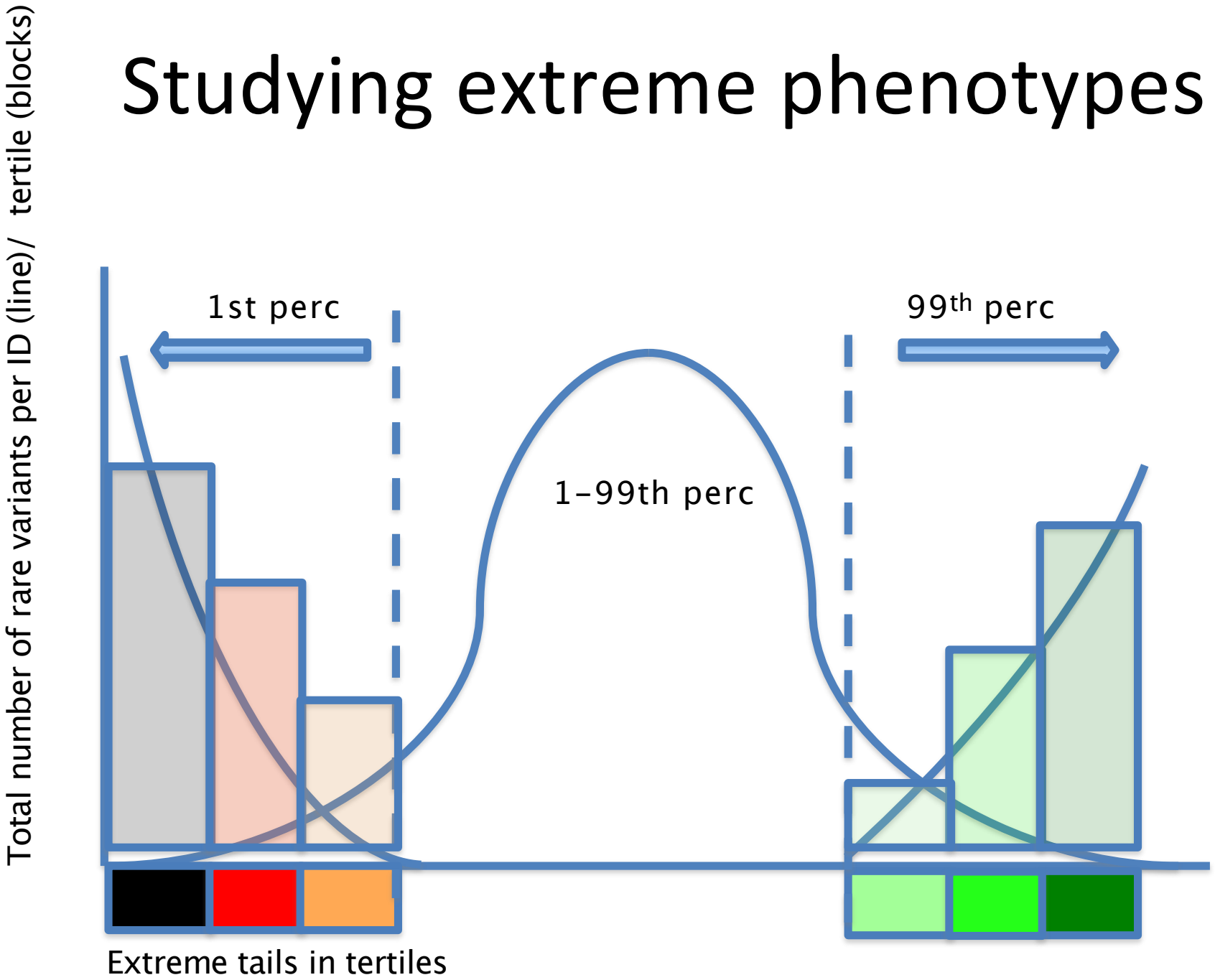


Take home messages

- Extreme genetics has proven helpful to find new routes to treat dyslipidemia
- Extreme low and high LDL-c remains to a significant extent unexplained

- To date, lipid-lowering drugs are prescribed to all patients at increased risk of CVD irrespective of age, gender, lifestyle
- Individualized care may e.g. be feasible when treatment options are very expensive

Studying extreme phenotypes



A family with FH of unknown etiology

European Journal of Human Genetics (2010) 18, 1236–1242

www.nature.com/ejhg

ARTICLE

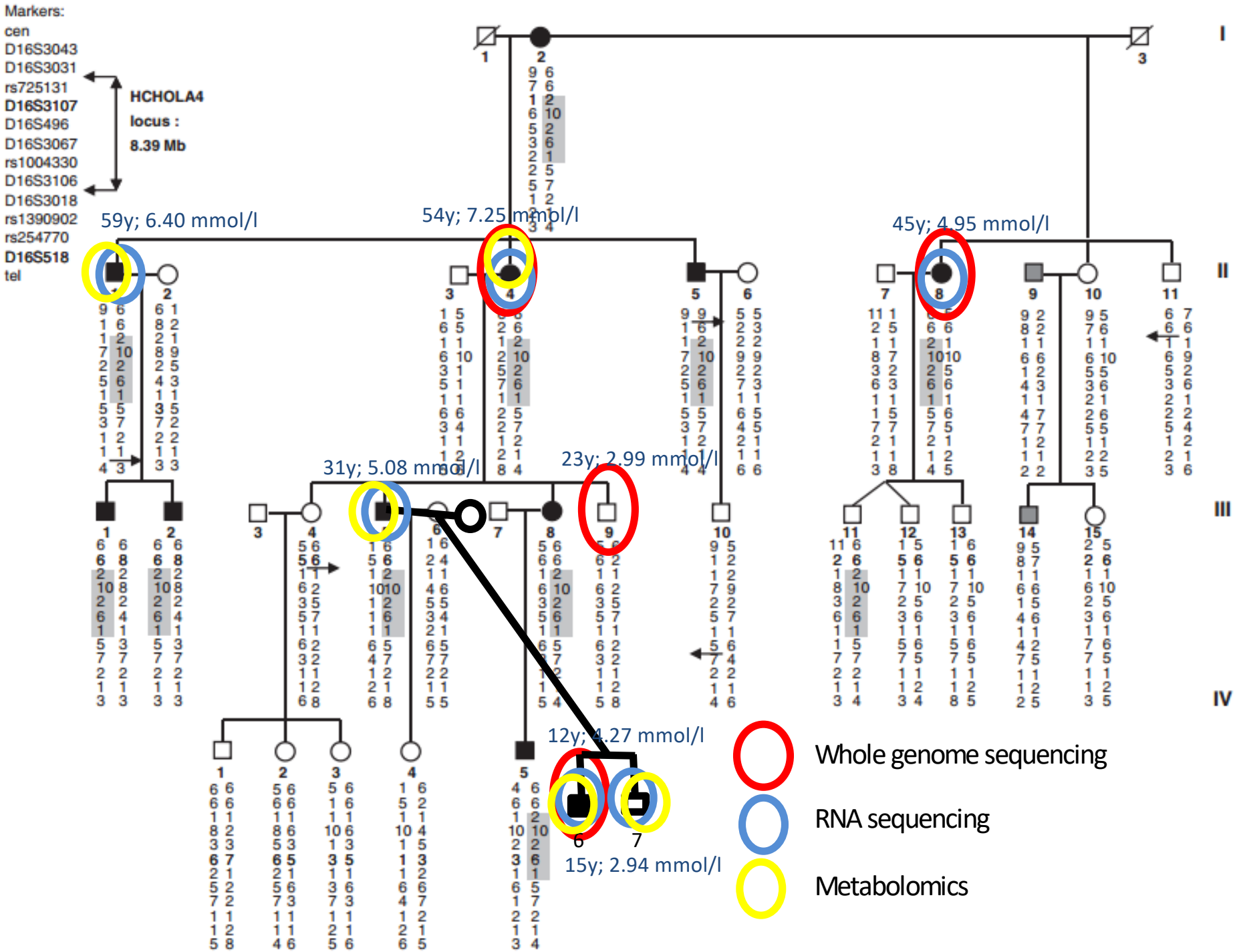
A fourth locus for autosomal dominant hypercholesterolemia maps at 16q22.1

Alice Marques-Pinheiro[1], Marie Marduel[1], Jean-Pierre Rabès[1,2], Martine Devillers[1], Ludovic Villéger[1], Delphine Allard[1], Jean Weissenbach[3], Maryse Guerin[4], Yassine Zair[5], Danièle Erlich[1], Claudine Junien[1], Arnold Munnich[1], Michel Krempf[5], Marianne Abifadel[1,6], Jean-Philippe Jaïs[7], The French Research Network on ADH[8], Catherine Boileau[1,2] and Mathilde Varret*[,1]

Autosomal dominant hypercholesterolemia (ADH) is characterized by isolated increase in plasmatic low-density lipoprotein (LDL) cholesterol levels associated with high risk of premature cardiovascular disease. Mutations in *LDLR*, *APOB*, and *PCSK9* genes have been shown to cause ADH. We now report further genetic heterogeneity of ADH through the study of a large French family in which the involvement of these three genes was excluded. A genome-wide scan mapped the disease-causing gene, named *HCHOLA4*, at 16q22.1 in a 7.89-Mb interval containing 154 genes with a maximum LOD score of 3.9. To reduce the linked region, we genotyped 18 smaller non-*LDLR*/non-*APOB*/non-*PCSK9*-ADH families at the *HCHOLA4* locus. Six families did not

Work performed

- No mutations candidate genes (exome seq)
- In vivo apoB kinetics – decreased LDL catabolism
- Fibroblasts
  - reduced number of LDL receptors at cell surface
  - LDLr trafficking appears delayed
- Proteomic analysis
  - overexpression RAB6A


Markers:
cen
D16S3043
D16S3031
rs725131
D16S3107
D16S496
D16S3067
rs1004330
D16S3106
D16S3018
rs1390902
rs254770
D16S518
tel
HCHOLA4
locus :
8.39 Mb
59y; 6.40 mmol/l
54y; 7.25 mmol/l
45y; 4.95 mmol/l
31y; 5.08 mmol/l
23y; 2.99 mmol/l
12y; 4.27 mmol/l
15y; 2.94 mmol/l
I
II
III
IV
Whole genome sequencing
RNA sequencing
Metabolomics

Genome wide associations and lipid levels

nature genetics

The impact of low-frequency and rare variants on lipid levels

Table 1: Newly identified loci associated with HDL-C, LDL-C, TC and/or TG concentrations

Locus	Chr.	Position B37	rsID	Annotation	Primary associated trait	Secondary associated trait	Alleles (effect/other)	EAF	Meta-analysis		
									Effect (SE)	*P*	*n*
PROX1	1	214,161,820	rs340839	5′ UTR	TG		A/G	0.47	0.039 (0.006)	4.4×10^{-10}	54,836
CEP68	2	65,284,623	rs2540948	Intronic	TG		C/T	0.35	−0.036 (0.006)	6.6×10^{-9}	59,939
PRKAG3	2	219,699,999	rs78058190	Intergenic	HDL-C		A/G	0.05	−0.141 (0.020)	5.7×10^{-12}	52,934
ADAMTS3	4	73,696,709	rs117087731	Intergenic	TC		T/A	0.01	0.308 (0.051)	2.3×10^{-9}	23,641
MTHFD2L	4	75,084,732	rs182616603	Intronic	TC		T/C	0.01	0.374 (0.044)	1.8×10^{-17}	42,905
MTHFD2L	4	75,084,732	rs182616603	Intronic		LDL-C	T/C	0.01	0.314 (0.045)	2.1×10^{-12}	38,420
GPR85	7	112,722,196	rs2255811	3′ UTR	TG		G/A	0.25	0.041 (0.007)	2.3×10^{-8}	59,962
RMI2	16	11,454,650	rs7188861	Intergenic	HDL-C		A/C	0.20	0.044 (0.008)	6.9×10^{-9}	60,578
TM4SF5	17	4,667,984	rs193042029	Intergenic	TG		G/T	0.01	−0.170 (0.029)	8.1×10^{-9}	50,105
GATA6	18	19,907,770	rs79588679	Intergenic	LDL-C		T/C	0.17	−0.049 (0.009)	3.6×10^{-8}	53,108
ZNF274	19	58,681,861	rs117492019	Intergenic	LDL-C		T/G	0.19	−0.047 (0.008)	1.2×10^{-8}	55,371
ZNF274	19	58,671,267	rs12983728	Intergenic		TC	A/G	0.16	−0.046 (0.008)	4.9×10^{-8}	58,904

Which genes or regulatory elements?

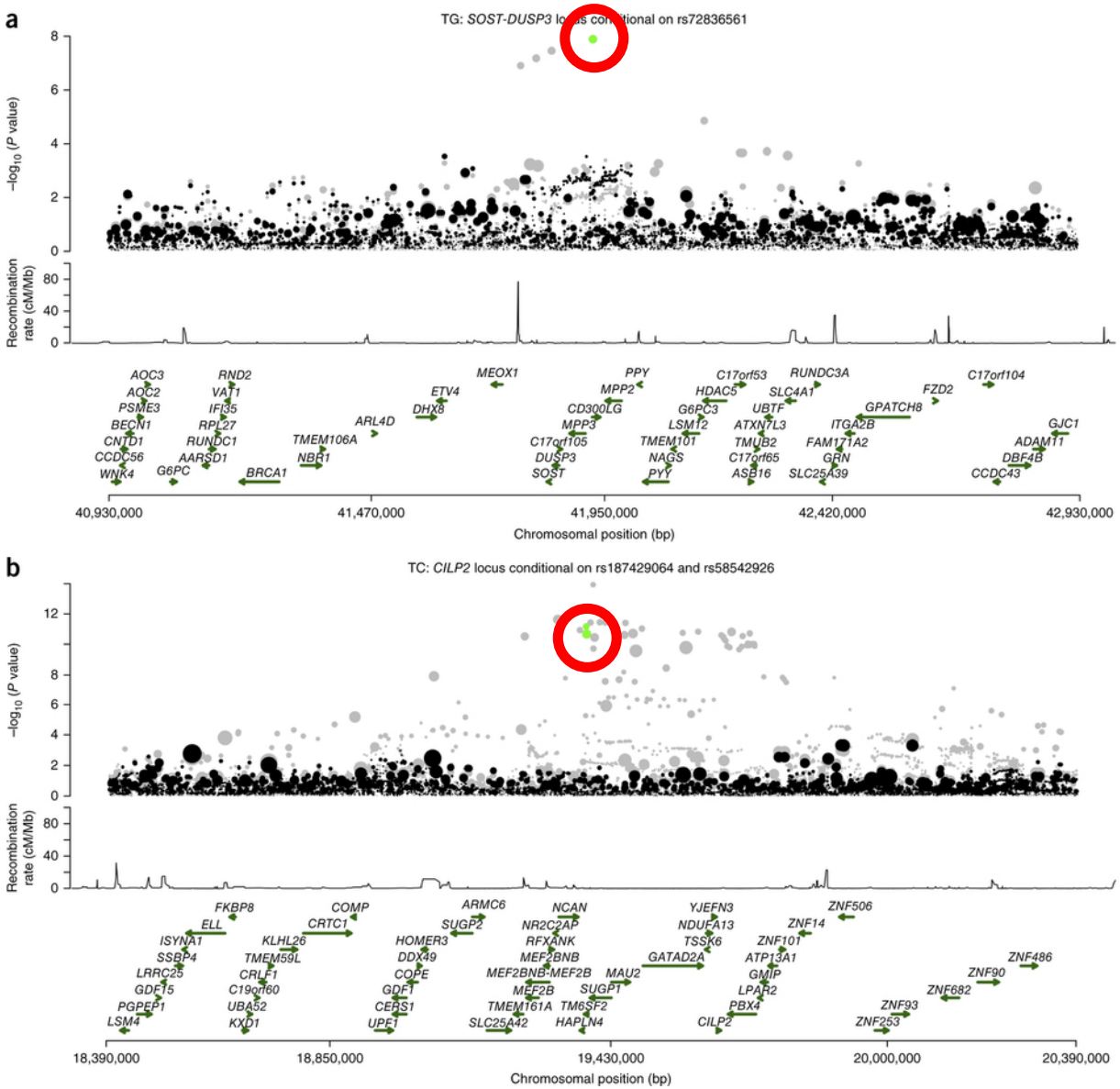


Figure 2: Regional association plots of the conditional analysis in loci where the new candidate functional SNPs explain the genome-wide association.

Genetic variantions and GWAS

university of groningen

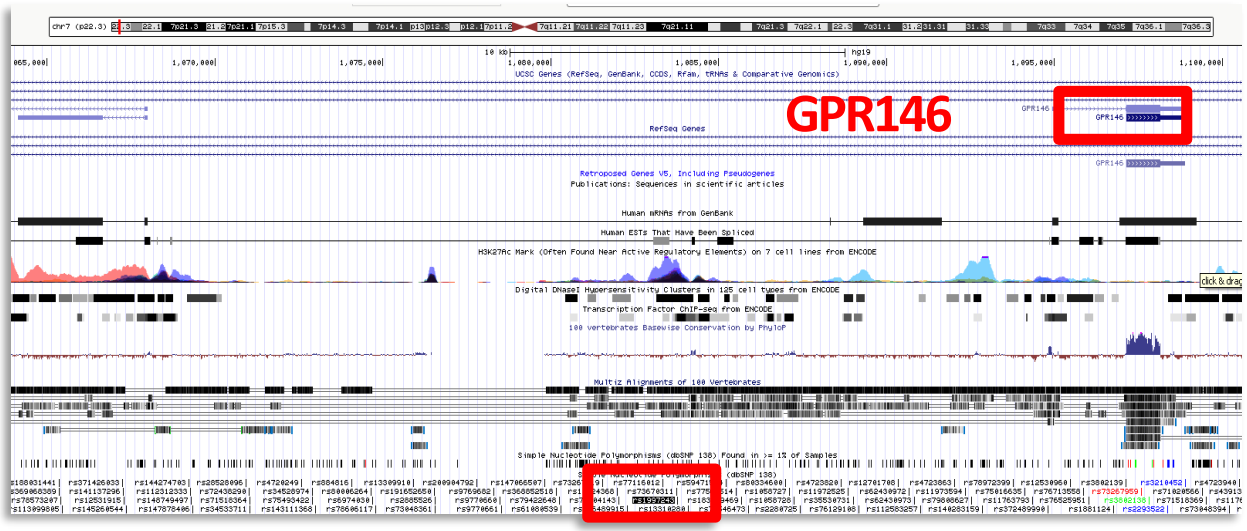
ARTICLES

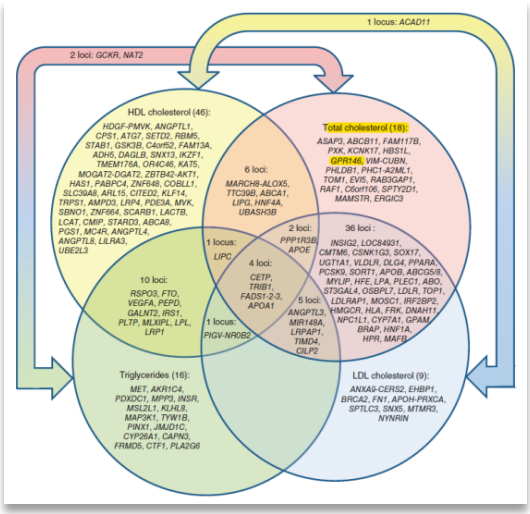
nature genetics

Discovery and refinement of loci associated with lipid levels

Global Lipids Genetics Consortium*

Levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides and total cholesterol are heritable, modifiable risk factors for coronary artery disease. To identify new loci and refine known loci influencing these lipids, we examined 188,577 individuals using genome-wide and custom genotyping arrays. We identify and annotate 157 loci associated with lipid levels at $P < 5 \times 10^{-8}$, including 62 loci not previously associated with lipid levels in humans. Using dense genotyping in individuals of European, East Asian, South Asian and African ancestry, we narrow association signals in 12 loci. We find that loci associated with blood lipid levels are often associated with cardiovascular and metabolic traits, including coronary artery disease, type 2 diabetes, blood pressure, waist-hip ratio and body mass index. Our results demonstrate the value of using genetic data from individuals of diverse ancestry and provide insights into the biological mechanisms regulating blood lipids to guide future genetic, biological and therapeutic research.

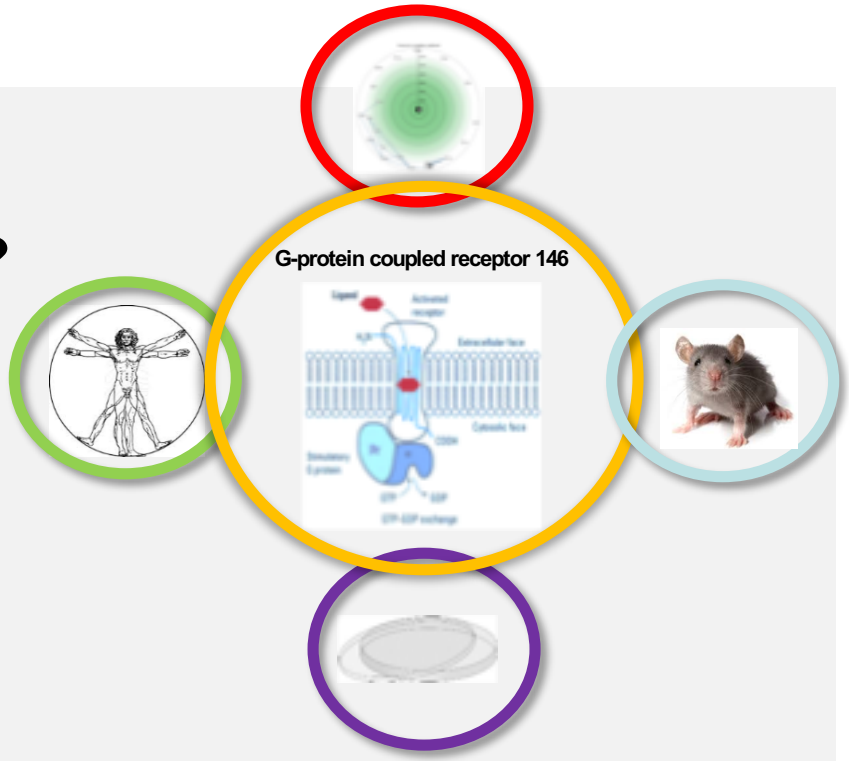




Research questions

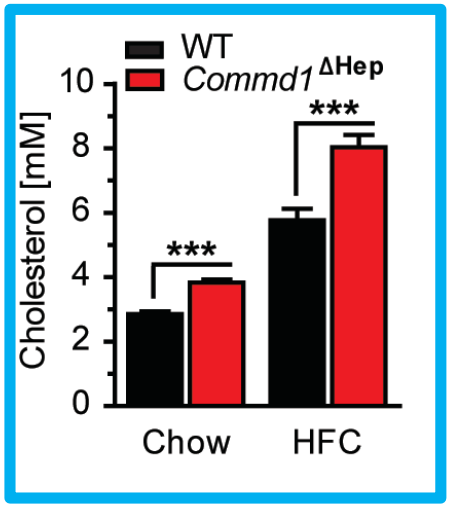
university of groningen

- What`s the role of Gpr146 in lipid homeostasis in mice and humans?

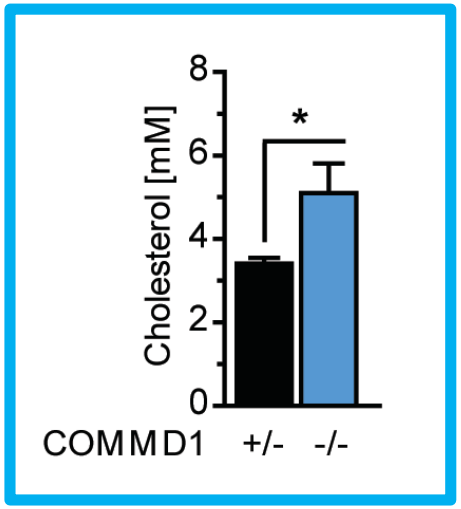


- Which are the mechanism(s) reducing cholesterol and TG?
- What`s the role of Gpr146 in atherosclerosis development?
- What`s the role of Gpr146 in glucose homeostasis ?
- Does genetic variation in *GPR146* associate with CVD endpoints?

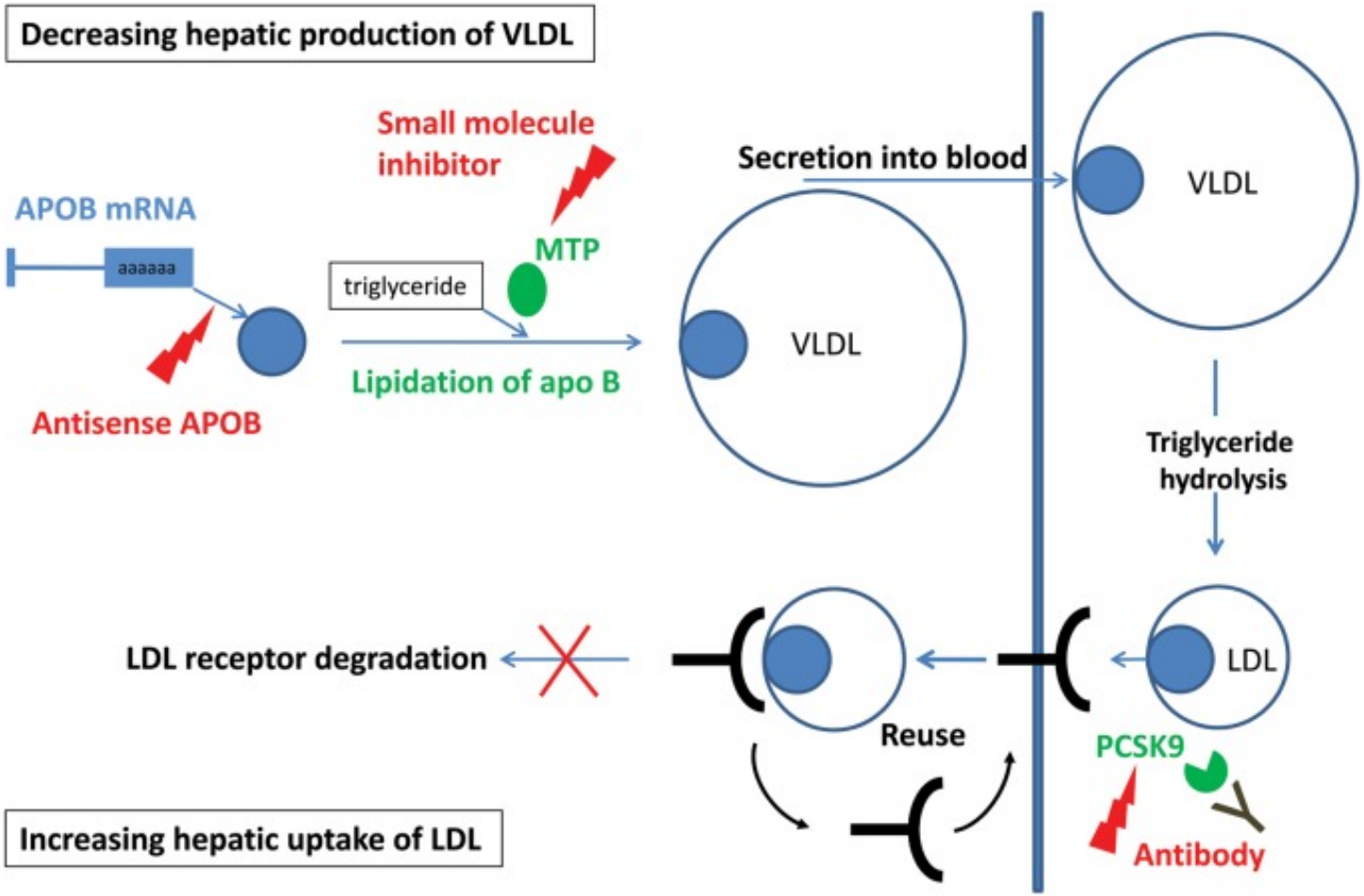
Commd1 deficiency - increased cholesterol



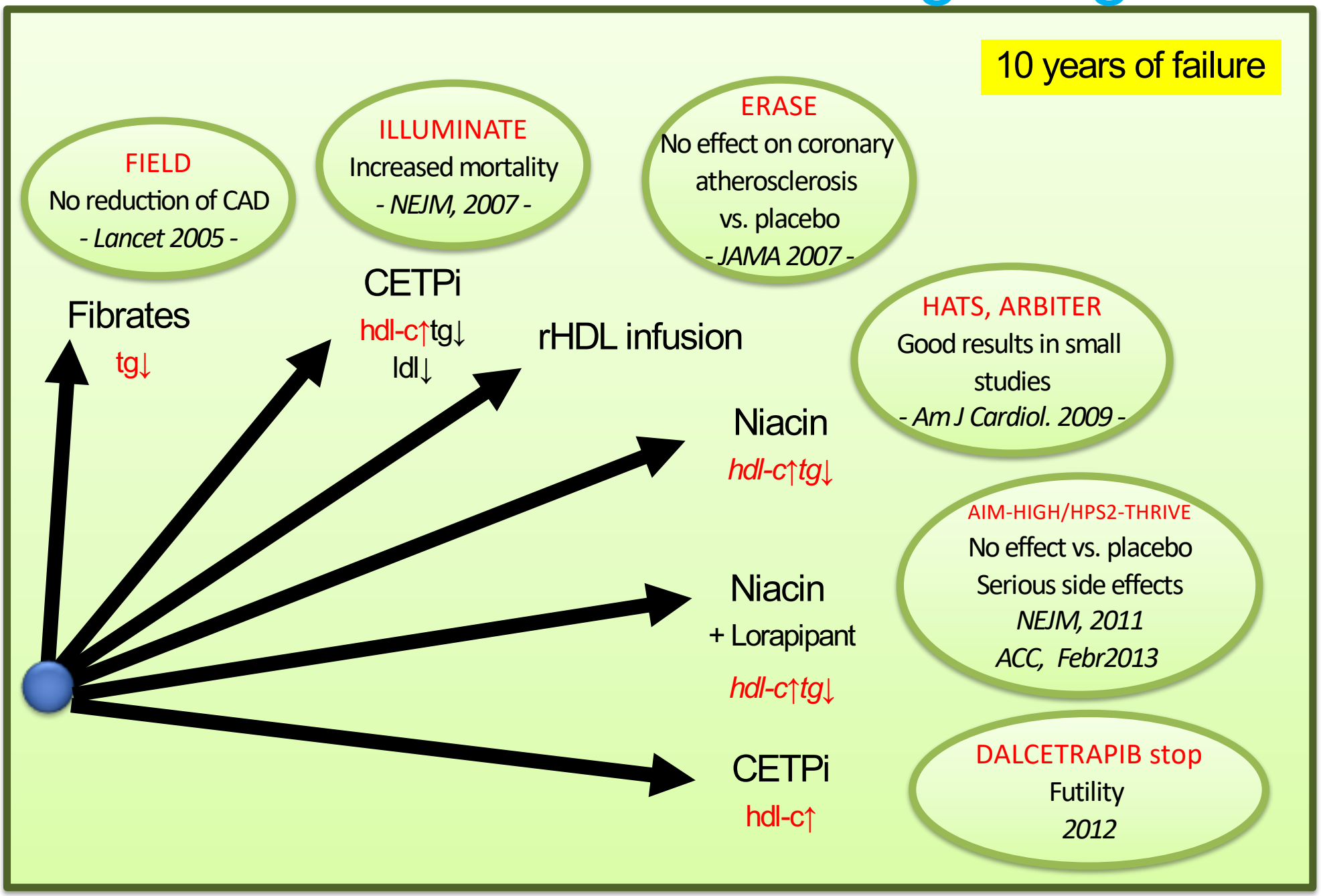
Beagleton dogs (Bedlington x Beagle);
Received from R.Favier



Treating FH

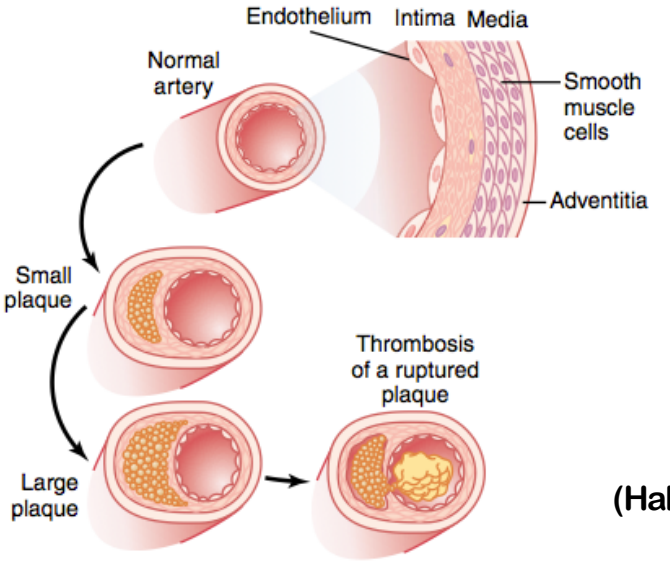

Decreasing hepatic production of VLDL
Small molecule inhibitor
APOB mRNA
aaaaaa
MTP
triglyceride
Lipidation of apo B
Antisense APOB
Secretion into blood
VLDL
VLDL
Triglyceride hydrolysis
LDL receptor degradation
LDL
Reuse
PCSK9
Antibody
Increasing hepatic uptake of LDL

TG and HDL modulating drugs

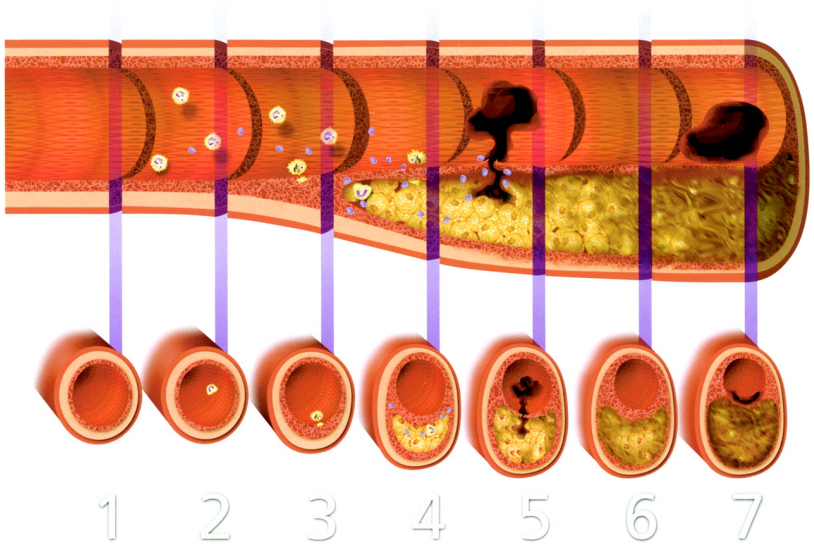


Atherogenesis

- Damage to the vascular endothelium wall
- Accumulation of monocytes-macrophages and LDLs
- Formation of fatty streak & plaque
- Plaque can burst and disrupt the artery, or remain as it is and still cause dysfunctions leading to cardiovascular disease



(Hall and Guyton)



Libby P *Circulation*. 2001;104:365-372