



The clinical and experimental laboratory in the study of rare dyslipidemia

**Advanced Course on Rare
Dyslipidaemia and Atherosclerosis
Importance of Personalized Medicine
and Differential Diagnosis**

October 19, 2018

*Bassini Hospital Via M. Gorki, 50
Cinisello Balsamo – Milan*

*Chairman
Alberico L. Catapano*

Maurizio Averna

DIBIMIS
Dipartimento iomedico di Medicina Interna e Specialistica
Università degli Studi di Palermo

EAS



Agenda

- ◆ Definition
- ◆ Hyper and Hypolipidemias
- ◆ The severe hypercholesterolemic phenotype
 - ADH-1, 2, 3
 - LDLRAP1
 - Beta-sitosterolemia
 - Cholesterol 7 alpha hydroxylase deficiency
- ◆ The severe hypertriglyceridemic phenotype

Dislipidemia/Hyperlipidemia

disorders of lipoprotein metabolism leading to abnormal high levels of plasma cholesterol and/or triglycerides

Primary (monogenic or polygenic)

caused by inherited genetic defects

Secondary

to an other condition, disease, drugs or wrong lifestyles

Hypolipidemias

disorders of lipoprotein metabolism leading to abnormal low levels of plasma cholesterol/ldl-c and/or hdl-c and/or triglycerides

LDL-C < 5th %- HDL-C < 10th %- TG < 10th%

Primary (monogenic or polygenic)

caused by inherited genetic defects
es. FHBL, FCH, LCAT deficiency

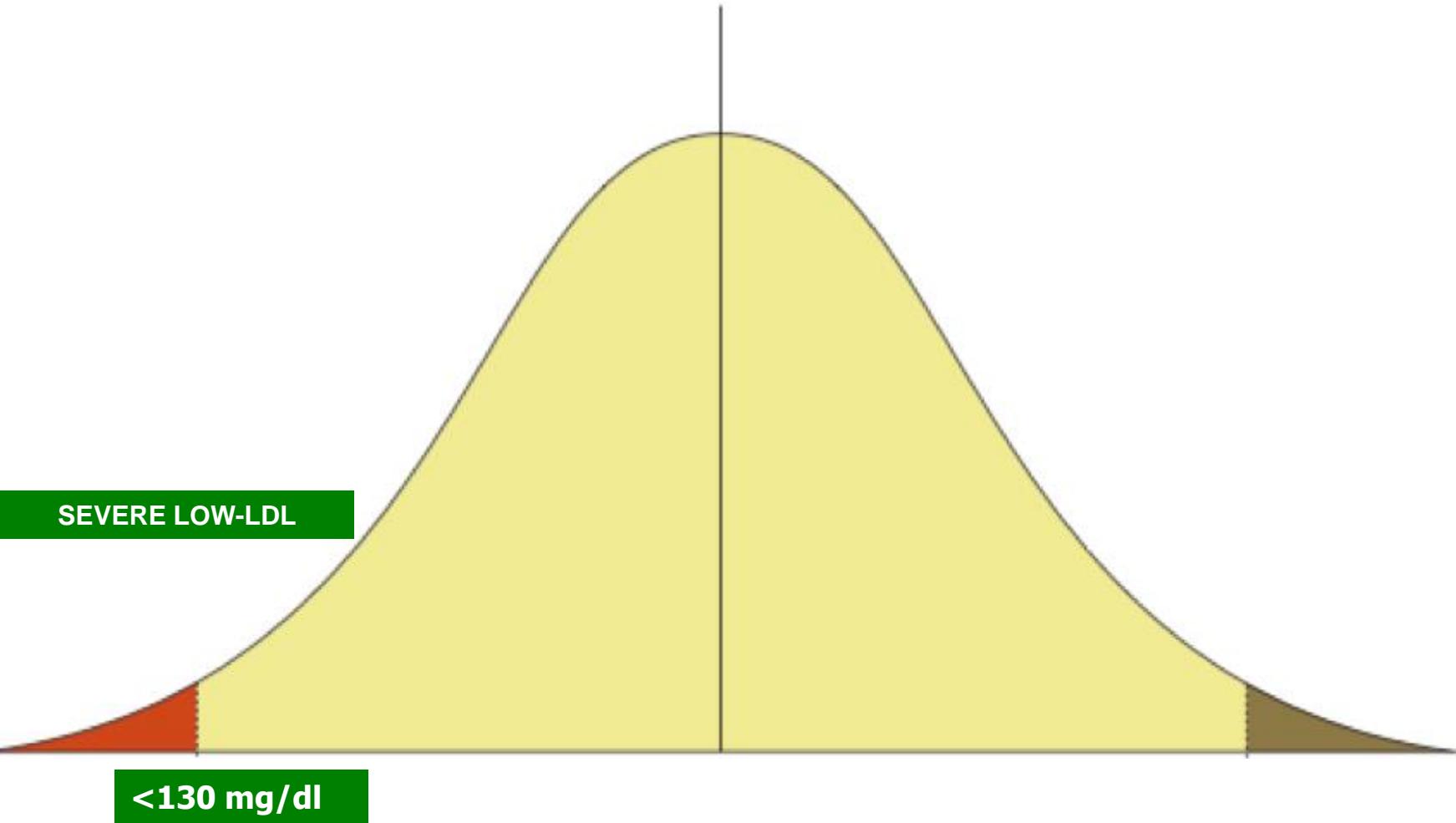
Secondary

to an other condition or disease

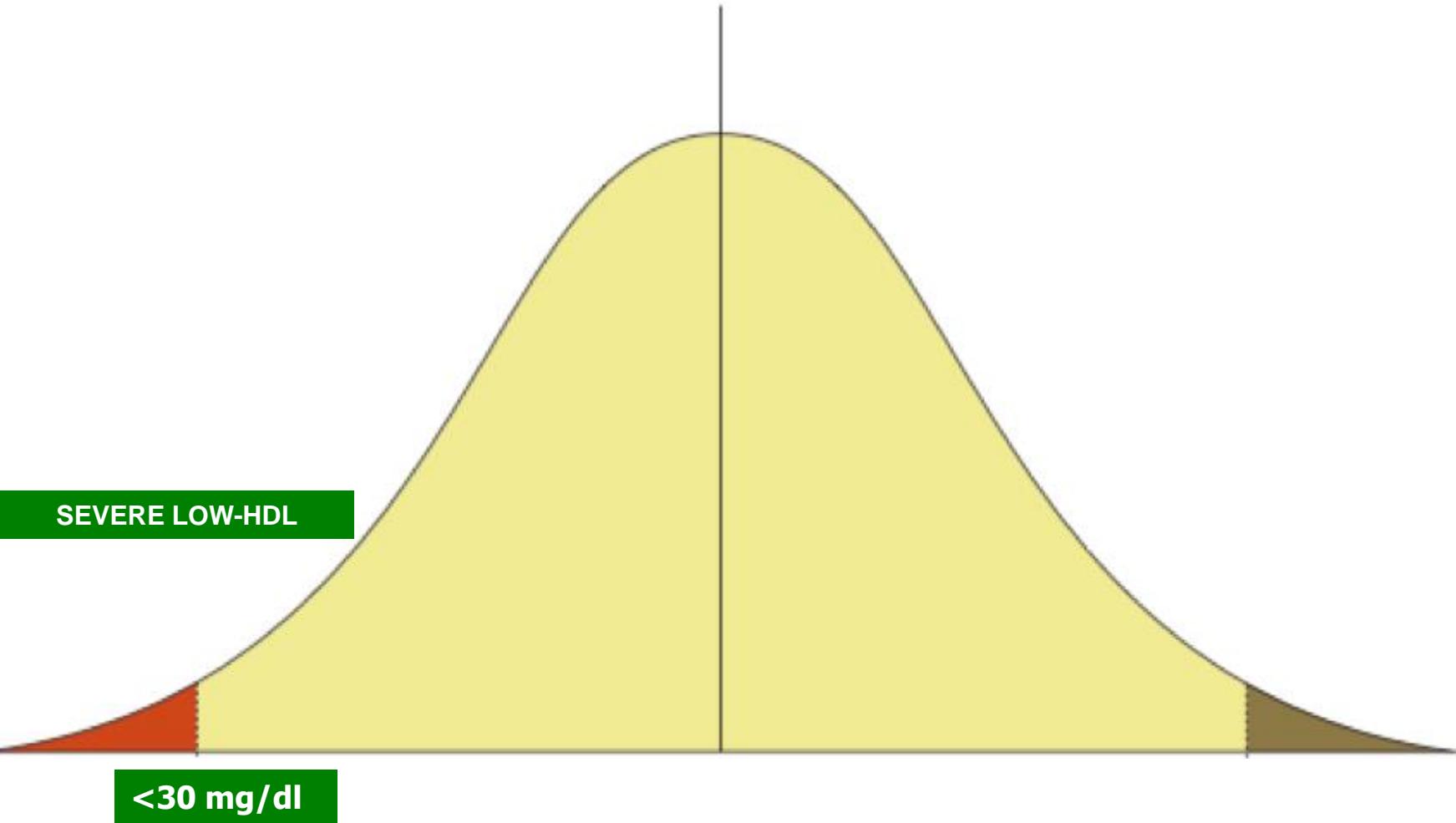
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DISTRIBUTION OF PLASMA CHOLESTEROL



DISTRIBUTION OF PLASMA HDL CHOLESTEROL

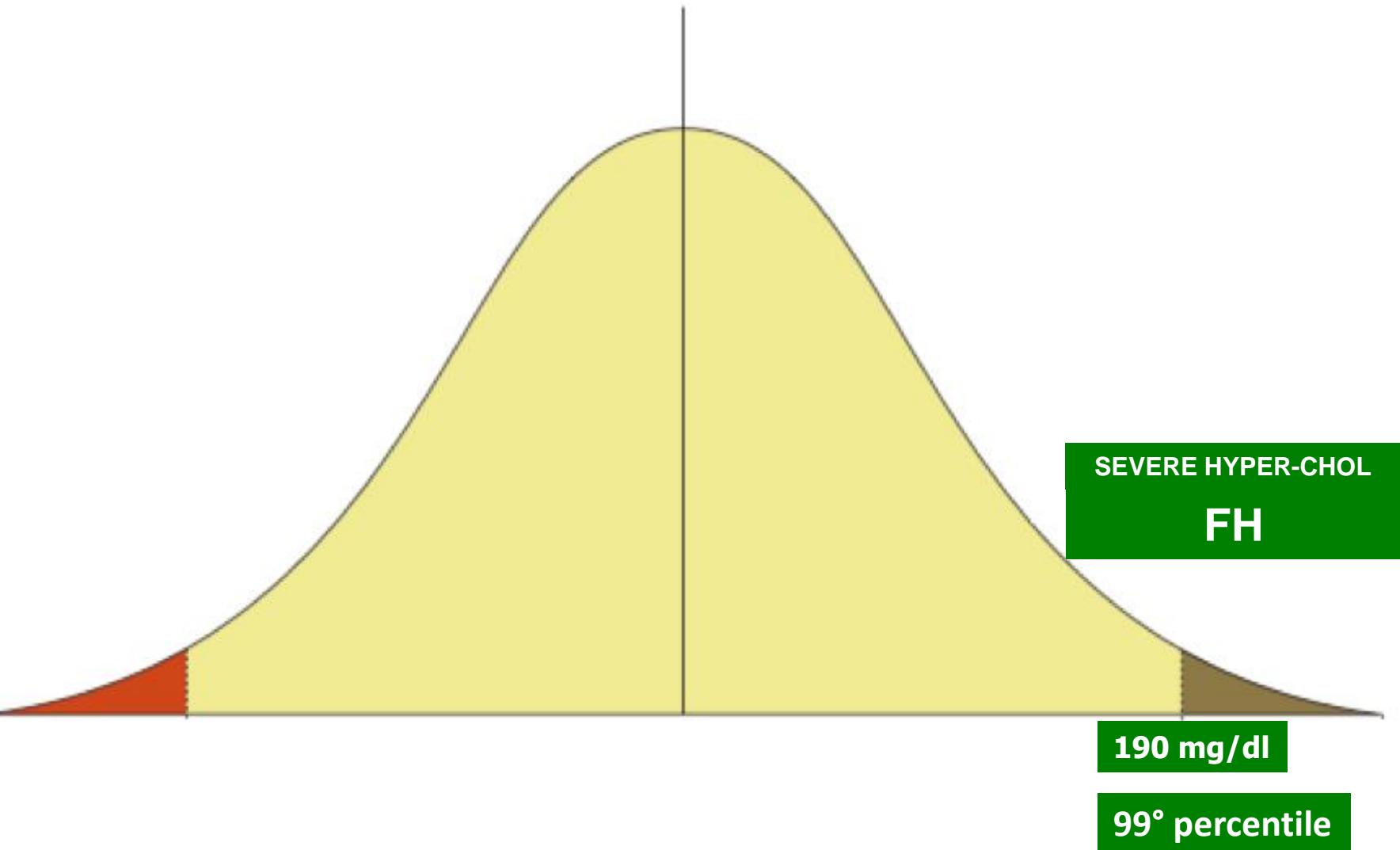


Possible Causes of Secondary Hypolipidemias

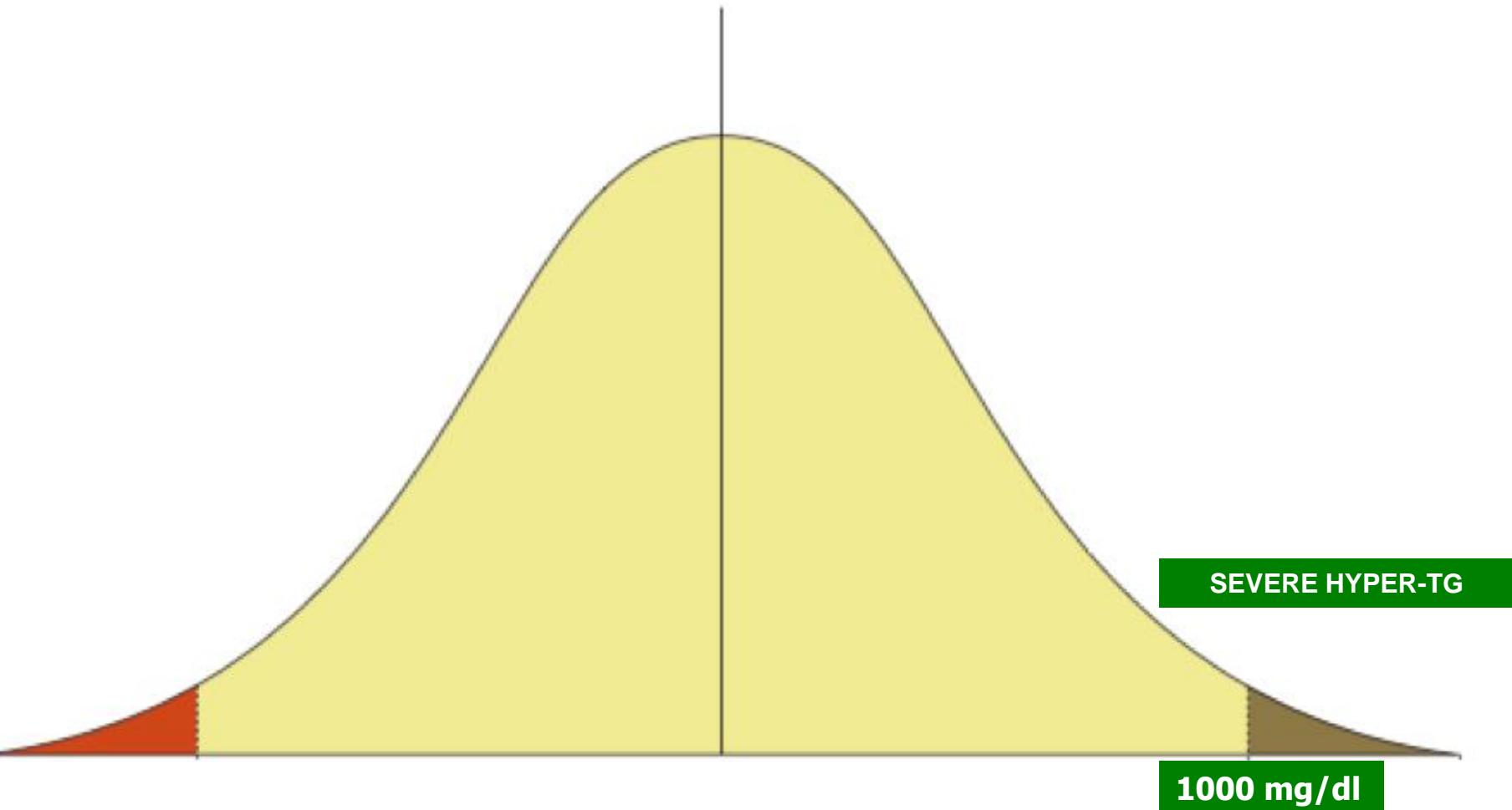
Diseases/Conditions

- Vegetarians
- Chronic parenchymal liver disease
- Chronic pancreatitis (adults)
- Cystic fibrosis (children)
- ESRD on hemodialysis
- Malnutrition and inflammation
- Hyperthyroidism
- Anemia (beta-thalassemia, sickle cell disease)
- Cancer

DISTRIBUTION OF PLASMA LDL CHOLESTEROL



DISTRIBUTION OF PLASMA TRIGLYCERIDES



Possible Causes of Secondary Hypercholesterolemias

Diseases

- Diabetes
- Hypothyroidism
- Nephrotic Syndrome
- Obstructive Liver Disease
- CKD

Drugs

- Progestins
- Corticosteroids
- Anabolic steroids
- β -blockers
- Thiazide diuretics
- Cyclosporin
- Sulfonylureas
- Isotretinoin
- Alcohol

Secondary causes and triggers of Hypertriglyceridemia

Lifestyle

Physical inactivity
High CHO intake (>60%)
Excessive alcohol

Medications

ERT/ OCP/ Tamoxifen
Steroids/Immunosuppressants
Beta-blockers/Thiazides
Retinoids
Protease inhibitors (HIV)
Atypical anti-psychotics

Associate Conditions

- Age
- Obesity
- MS/Diabetes
- Nefrotic Sindrome
- CKD
- Cushing
- Lipodistrofy
- Hypotiroidism
- Pregnancy

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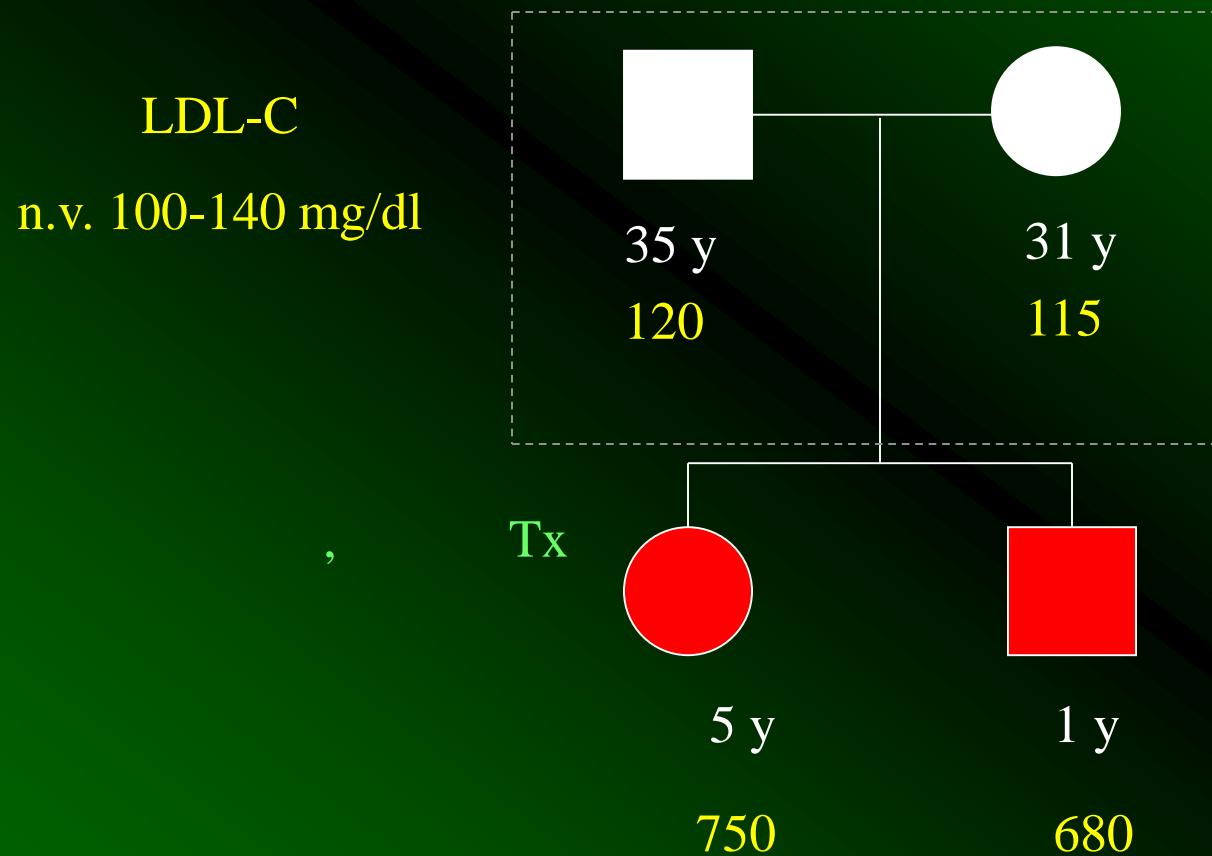
PRIMARY HYPERCHOLESTEROLEMIA

- High levels of LDL-Cholesterol (LDL-C) in plasma (>90° percentile).

with or without:

- Tendineous and Cutaneous Xanthomatosis,
- Arcus Cornealis
- **Premature Atherosclerosis (Coronary Heart Disease)**

RECESSIVE HYPERCHOLESTERolemia





INHERITED MONOGENIC HYPERCHOLESTEROLEMIAS

Dominant transmission

- Heterozygote LDL-C ↑↑
(One mutant allele)
- Homozygote LDL-C ↑↑↑↑↑
(Two mutant alleles)
- Gene dosage effect

Recessive transmission

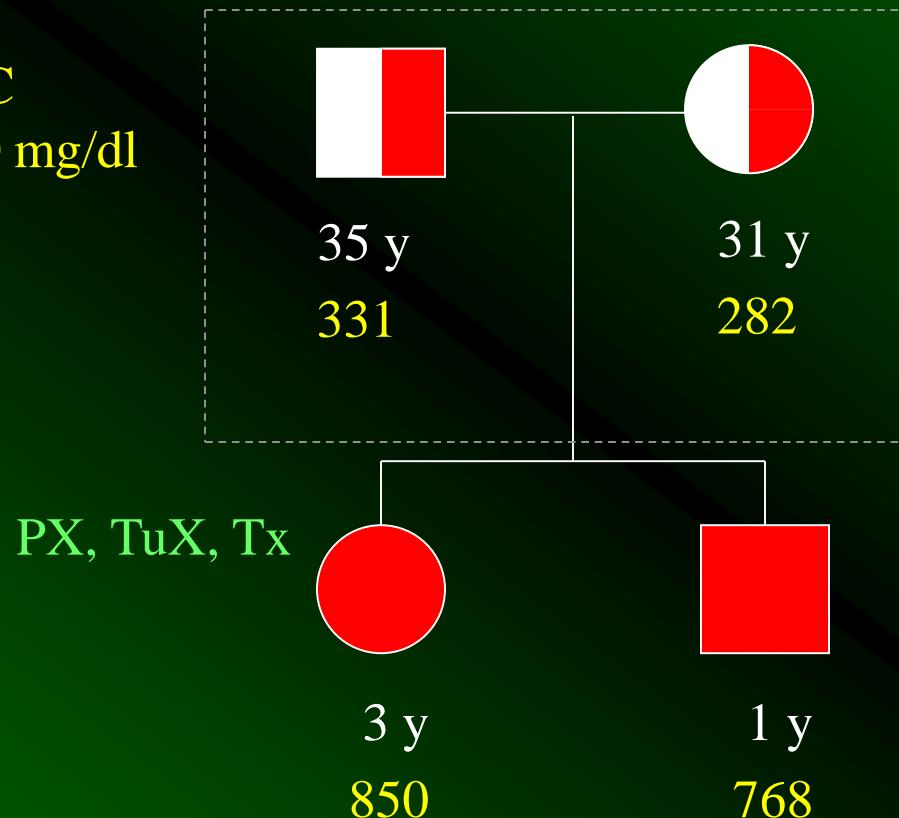
- Heterozygote LDL-C ↔
(One mutant allele)
- Homozygote LDL-C ↑↑↑
(Two mutant alleles)

Marked Monogenic Elevation in LDL Cholesterol are responsible for Familial Hypercholesterolemia

Gene	Disease	Inheritance	Frequency
LDL receptor	ADH-1	Autosomal dominant	1 in 250
Apolipoprotein B	ADH-2	Autosomal dominant	~ 1 in 1000 (IT) 1 in 250 (CE)
PCSK9	ADH-3	Autosomal dominant	rare
LDLRAP1	Autosomal recessive hypercholesterolemia ARH	Autosomal recessive	rare 1 in 140 (Sardinia)
CYP71a	Cholesterol 7 alpha hydroxylase deficiency	Autosomal recessive	rare
ABCG5/8	Sitosterolemia	Autosomal recessive	rare

DOMINANT HYPERCHOLESTEROLEMIA

LDL-C
n.v. 100-140 mg/dl



PX = Planar xanthomas

TuX = Tuberous Xanthoma, TX = Tendon xanthomas

Familial hypercholesterolemia (FH-ADH)

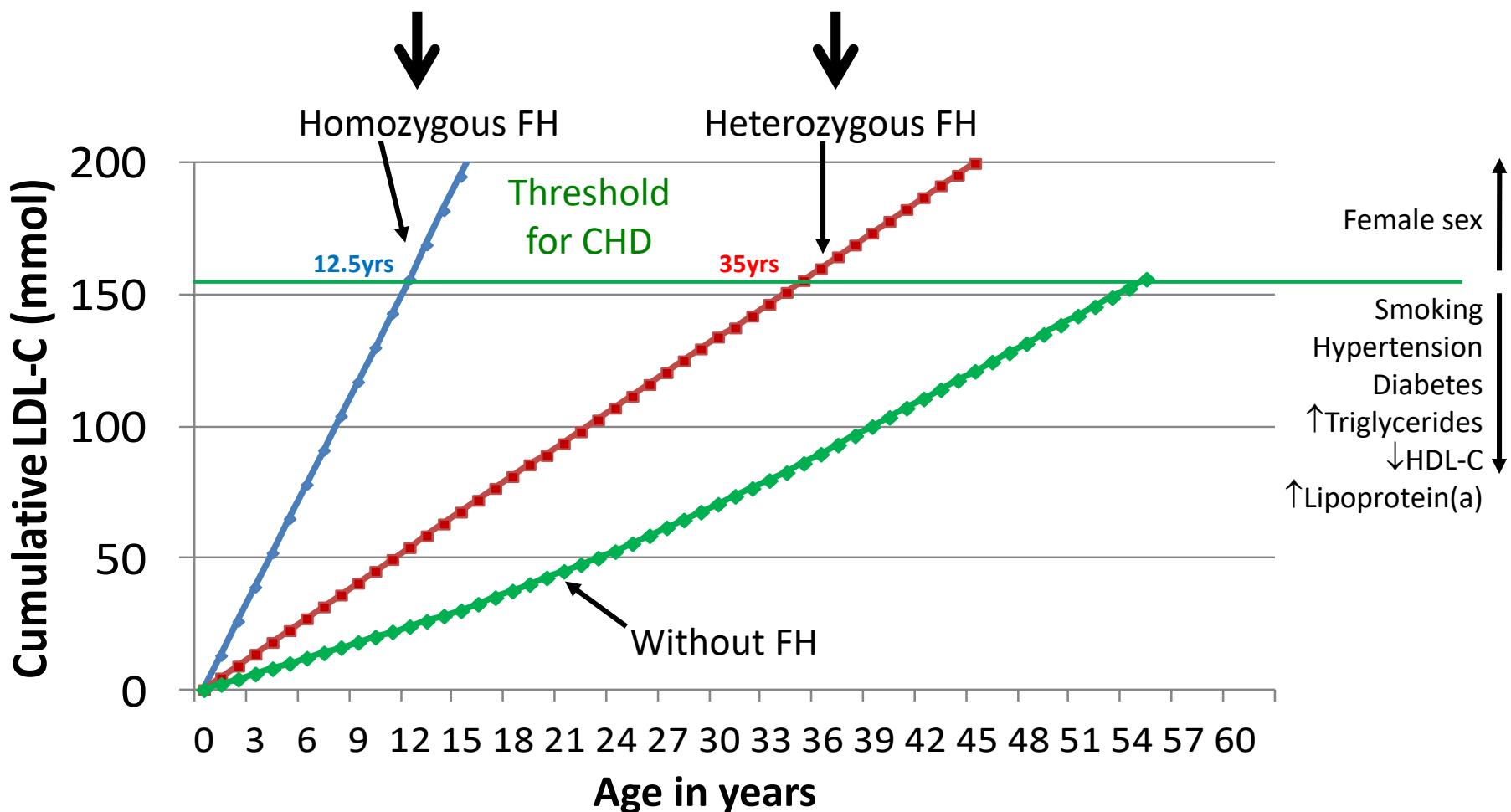
- Inheritable, autosomal co-dominant disorder
- usually due to mutations in *LDLR* gene
 - >2000 mutations
- two forms:
 - HoFH (1/3-400000): LDL-C > 500 mg/dl
 - HeFH (1/250): LDL-C > 190 mg/dl
- premature CVD events/death
- family history of premature CVD

FH exposes patients to high cholesterol from birth, with CHD earlier in life

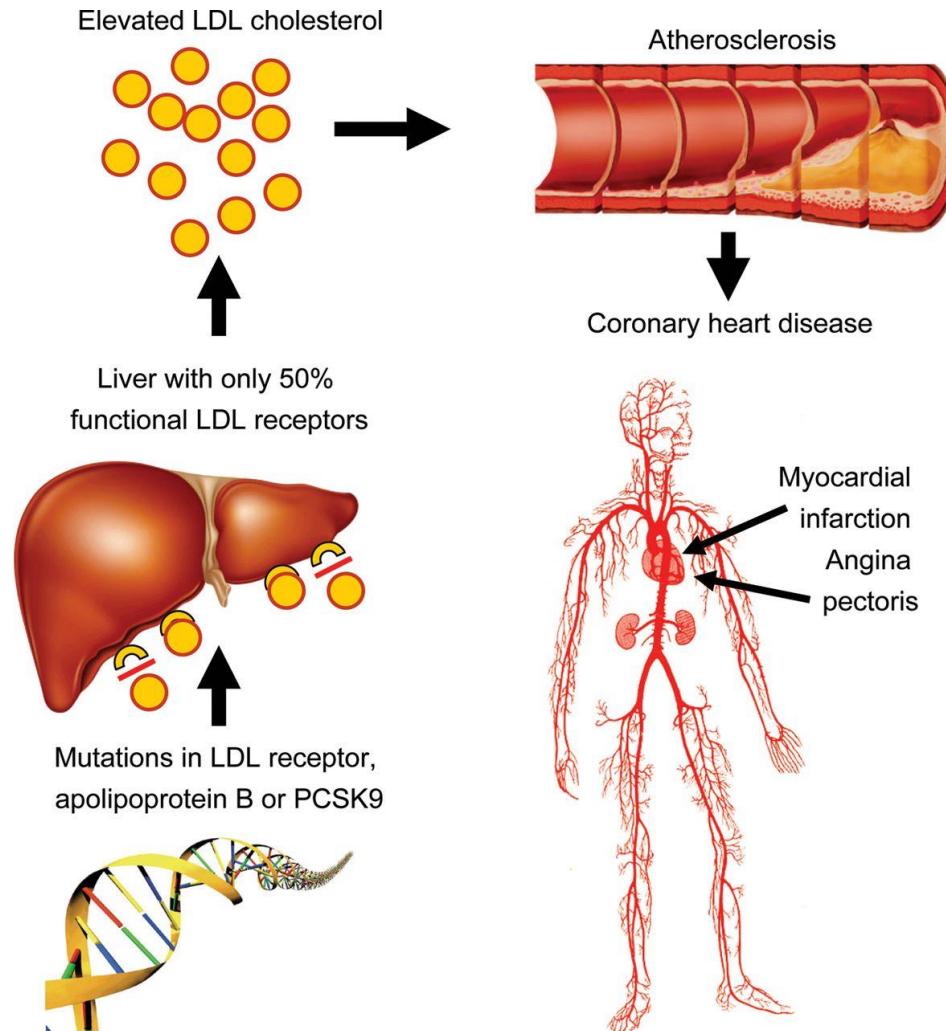
Cumulative exposure (cholesterol-yrs) by age:
FH vs. unaffected (healthy) individuals

Coronary disease & death before age 20

Untreated: coronary disease before age 55

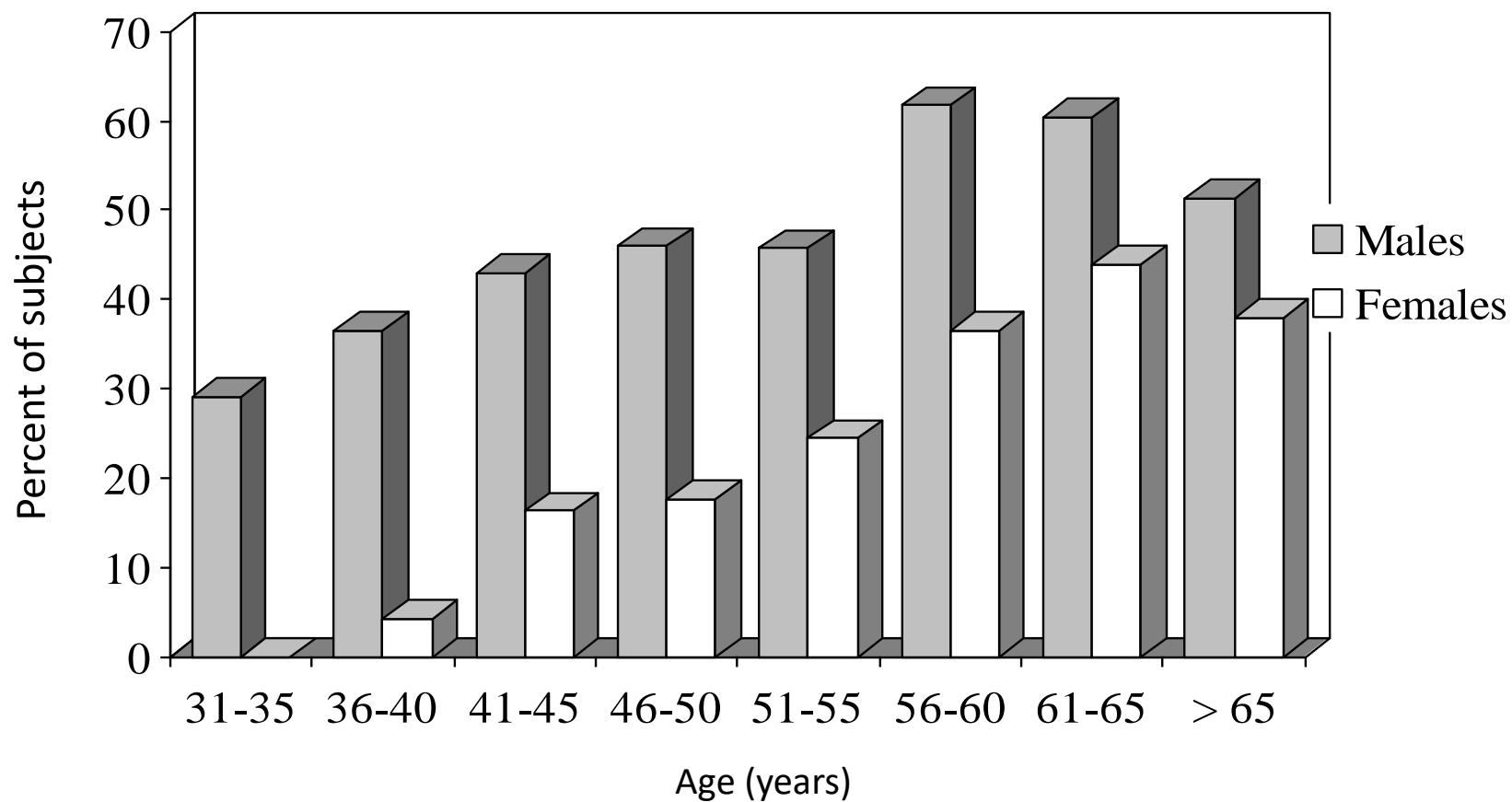


Pathophysiology of heterozygous familial hypercholesterolaemia.



Nordestgaard B G et al. Eur Heart J 2013;34:3478-3490

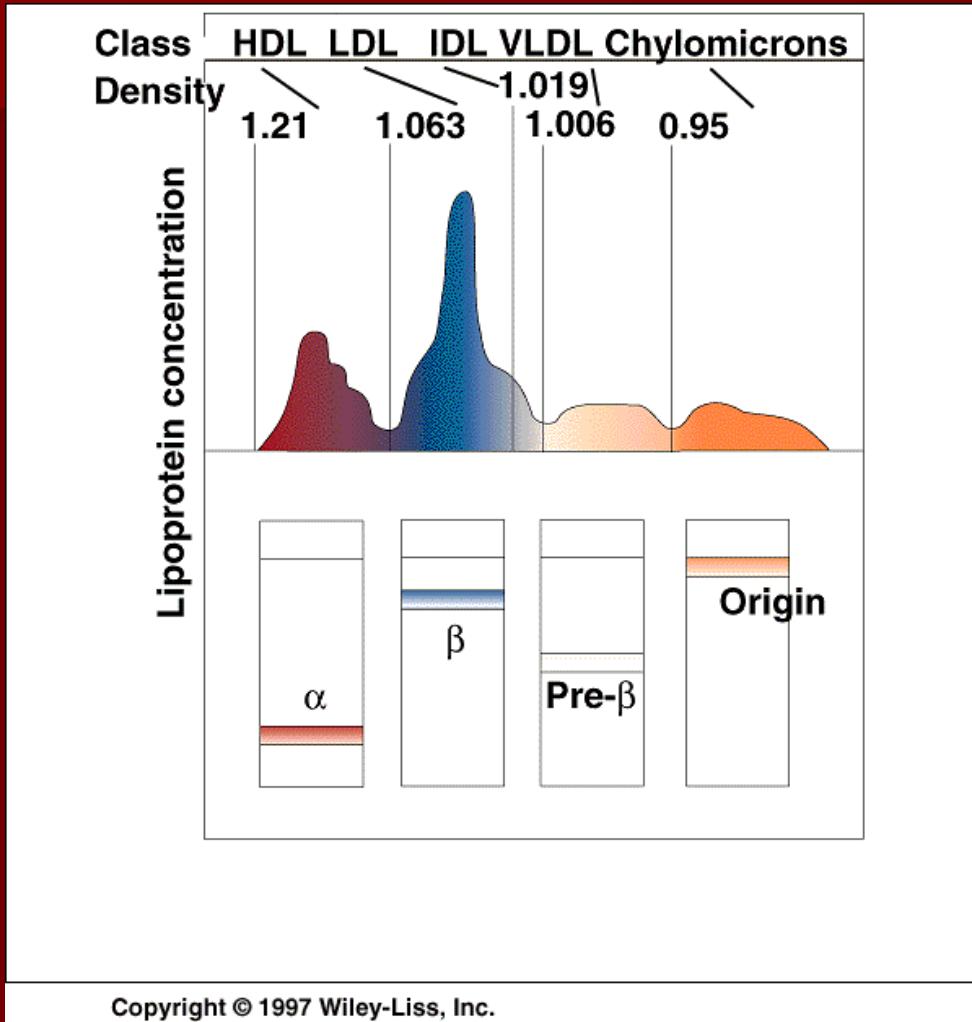
Percent prevalence of coronary heart disease in heterozygous ADH-1 patients over 30 years of age (476 males and 568 females) carrying pathogenic mutations of *LDLR* gene.



pCHD [M < 55 y 39.2 %
F < 65 y 20.5 %] P <0.0001

The biochemical diagnosis

Classification of Lipoproteins



Density

Electrophoresis

FORMS OF HYPERLIPOPROTEINEMIA DEFINED BY THE INCREASE OF LIPOPROTEIN CLASSES

TYPE	KILOs
I	LDL
IIA	LDL e VLDL
IIB	Beta-VLDL
III	VLDL
IV	VLDL e KILOs
V	

CARATTERISTICHE E COMPOSIZIONE DELLE LIPOPROTEINE PLASMATICHE

	Chilomicroni	VLDL	IDL	LDL	HDL ₂	HDL ₃	Lp(a)
<i>Caratteristiche fisiche</i>							
Densità (g/ml)	<0,95	0,95-1,006	1,006-1,019	1,019-1,063	1,063-1,125	1,125-1,210	1,05-1,12
Diametro (nm)	80-1000	30-80	25-30	19-25	8-11	6-9	23-26
Mobilità elettroforetica	origine	pre-beta	pre-beta lente	beta	alfa	alfa	prebeta lente
<i>Composizione chimica (% peso secco)</i>							
Proteine	1-2	6-10	12-16	20-25	35-40	45-55	29
Fosfolipidi	2-8	12-18	15-22	20-25	30-40	25-35	22
Colesterolo libero	1	5-8	7-11	6-10	4-6	1-3	10
Colesterolo esterificato	1-3	8-14	20-35	35-45	15-20	10-18	36
Trigliceridi	90-96	50-65	25-40	6-12	3-8	3-6	3
<i>Composizione apolipoproteica (%)</i>							
A-I	33	2	—	—	65	62	—
A-II	tracce	tracce	—	—	10	23	—
A-IV	14	—	—	—	—	tracce	—
B	5 (B48)	30-40	70-80	90-95	—	—	variabile
C	32	40-50	4-8	2	10-15	5	—
E	10	15	10-15	3	3	1	—
Altre	6	5	5	5	4	5	apo(a)

CARATTERISTICHE E FUNZIONI DELLE APOLIPOPROTEINE

Apolipo-proteina	Peso molecolare	Numero aminoacidi	Concentrazione plasmatica	Sintesi	Cromosoma	Funzione
A-I	28000	243	100-150 mg/dl	I,F	11	Strutturale Attivazione LCAT Legame recettore A-I
A-II	17500 (dimero)	154	30-50 mg/dl	F	1	Strutturale Attivazione lipasi epatica
A-IV	44500	376	15 mg/dl	I,F	11	Attivazione LCAT
B-100 (LDL)	513000	4536	70-120 mg/dl	F	2	Legame recettori apo B,E Strutturale
B-48	241000	2152	5 mg/dl	I	2	Strutturale
C-I	6500	57	4-10 mg/dl	F	19	Attivatore LCAT, LPL (?)
C-II	8500	73	3-5 mg/dl	F	19	Attivatore LPL
C-III	8750	79	8-15 mg/dl	F	11	Inibitore LPL Attivatore LCAT Modulazione captazione remnants (?)
D (A-III)	19500	169	5-10 mg/dl	?	3 (Cofattore LCAT)	(Trasporto colesterolo)
E	34000	299	2-7 mg/dl	F,M,C,S,G G,R,MS,MΦ	19	Legame recettore apo B,E Formazione HDL-1 Metabolismo Sist. Nervoso Centrale
Apo(a)	300000-700000	variabile	2 mg/dl *	F	6	(Interazione col sistema coagulativo)

LCAT = Lecitina-Colesterolo Acil Transferasi; LPL = Lipasi Lipoproteica; I = Intestino; F = Fegato; M = Milza; C = Cervello; S = Surreni; G = Gonadi; R = Rene; MS = Muscolo Striato; MΦ = Macrfagi.

Carta di Identità

Foto

Nome: Low Density Lipoprotein

Nickname: LDL

Occupazione: Cholesterol Carrier

Caratteristiche: particella sferica

Dimensioni: Diametro 220 nm
Massa ~3000 kDa

Composizione:

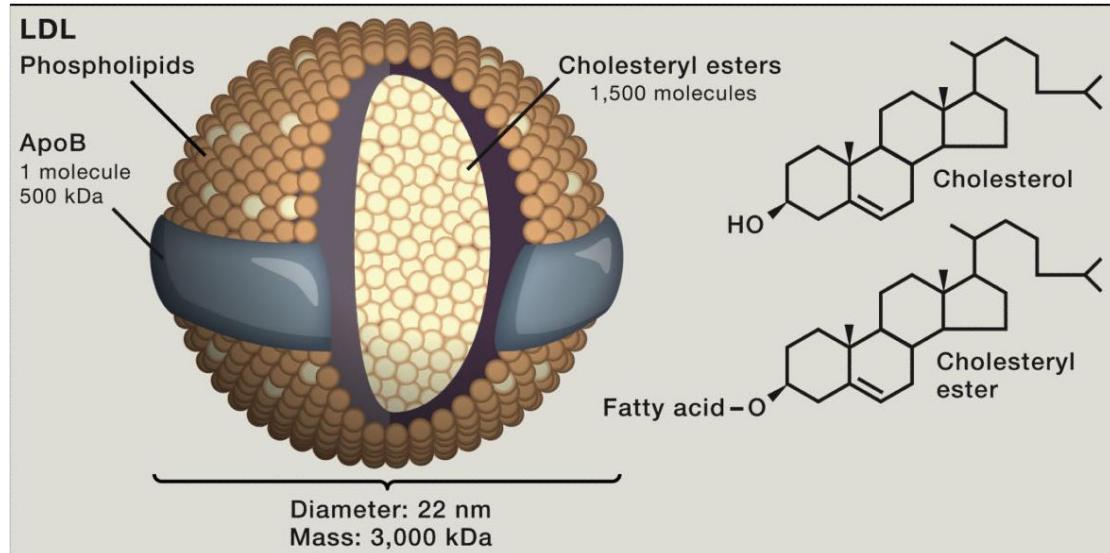
~1500 molecole di CE

protette dal mezzo acquoso da un mantello idrofilico composto da:

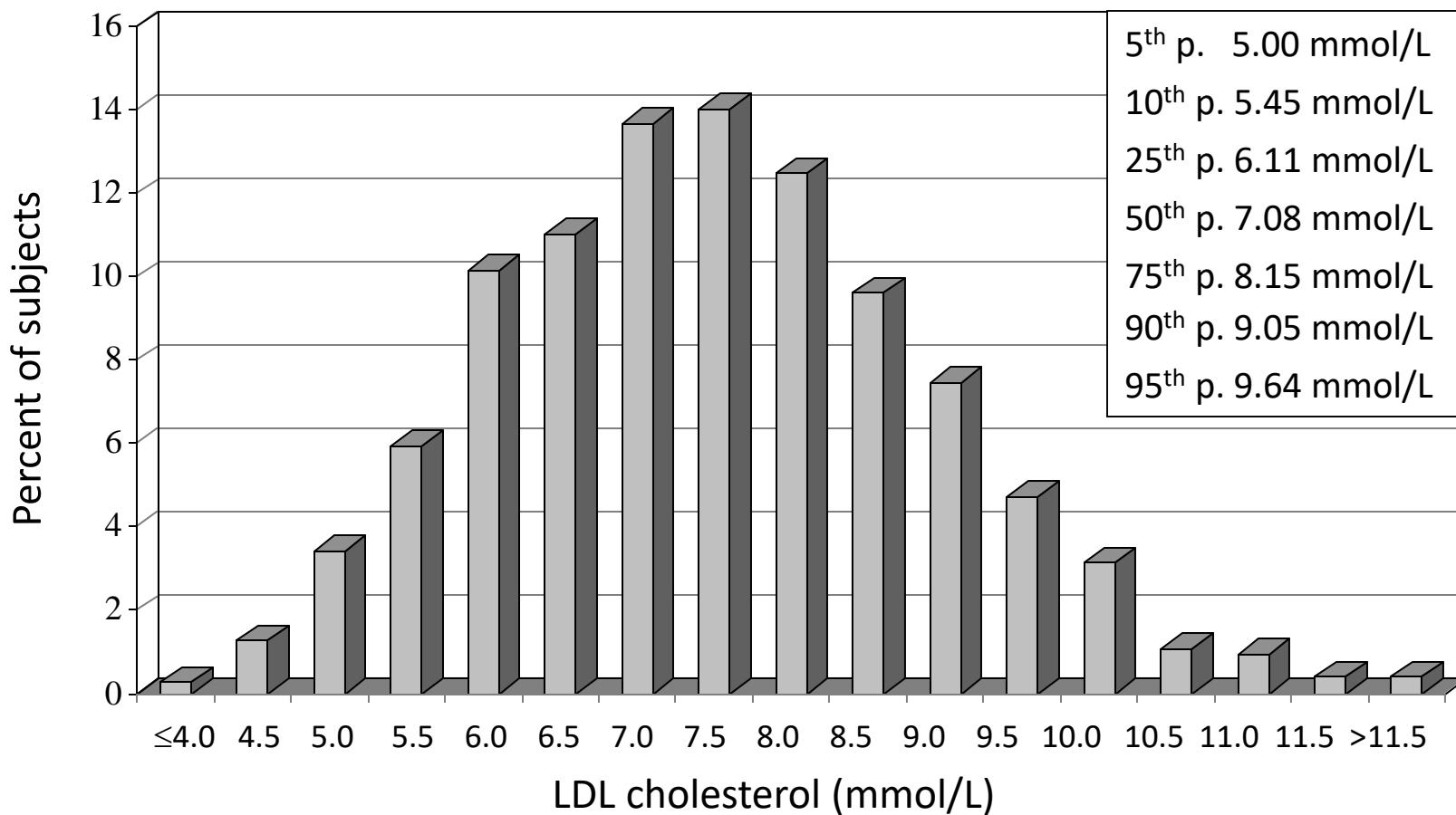
~800 molecole di fosfolipidi

~500 molecole di FC

1 molecola di apoB (massa 500 kDa)

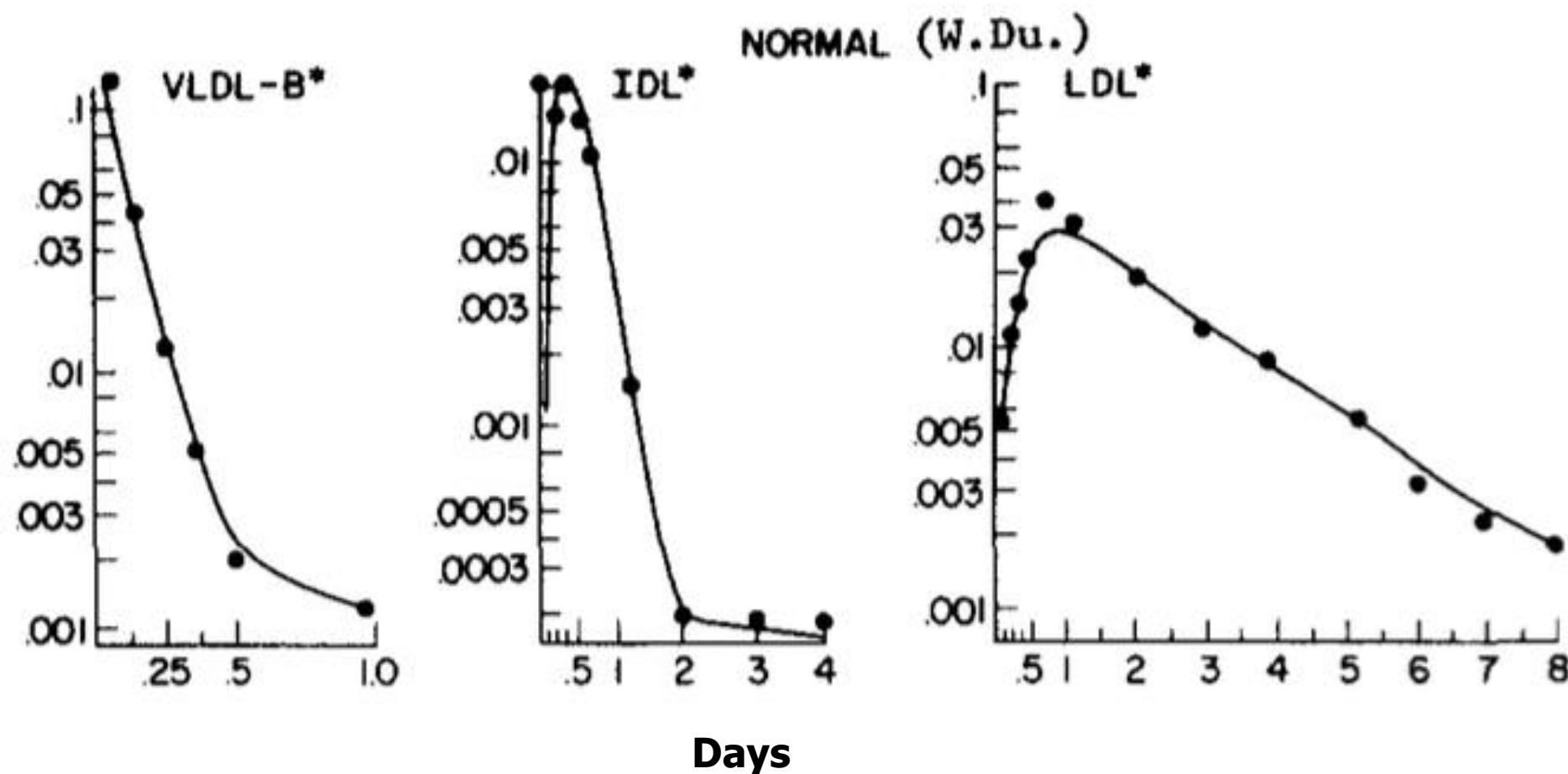


Distribution of LDL cholesterol levels (adjusted for gender, age and familial relations) in 1769 ADH-1 heterozygous patients carrying pathogenic mutations of *LDLR* gene

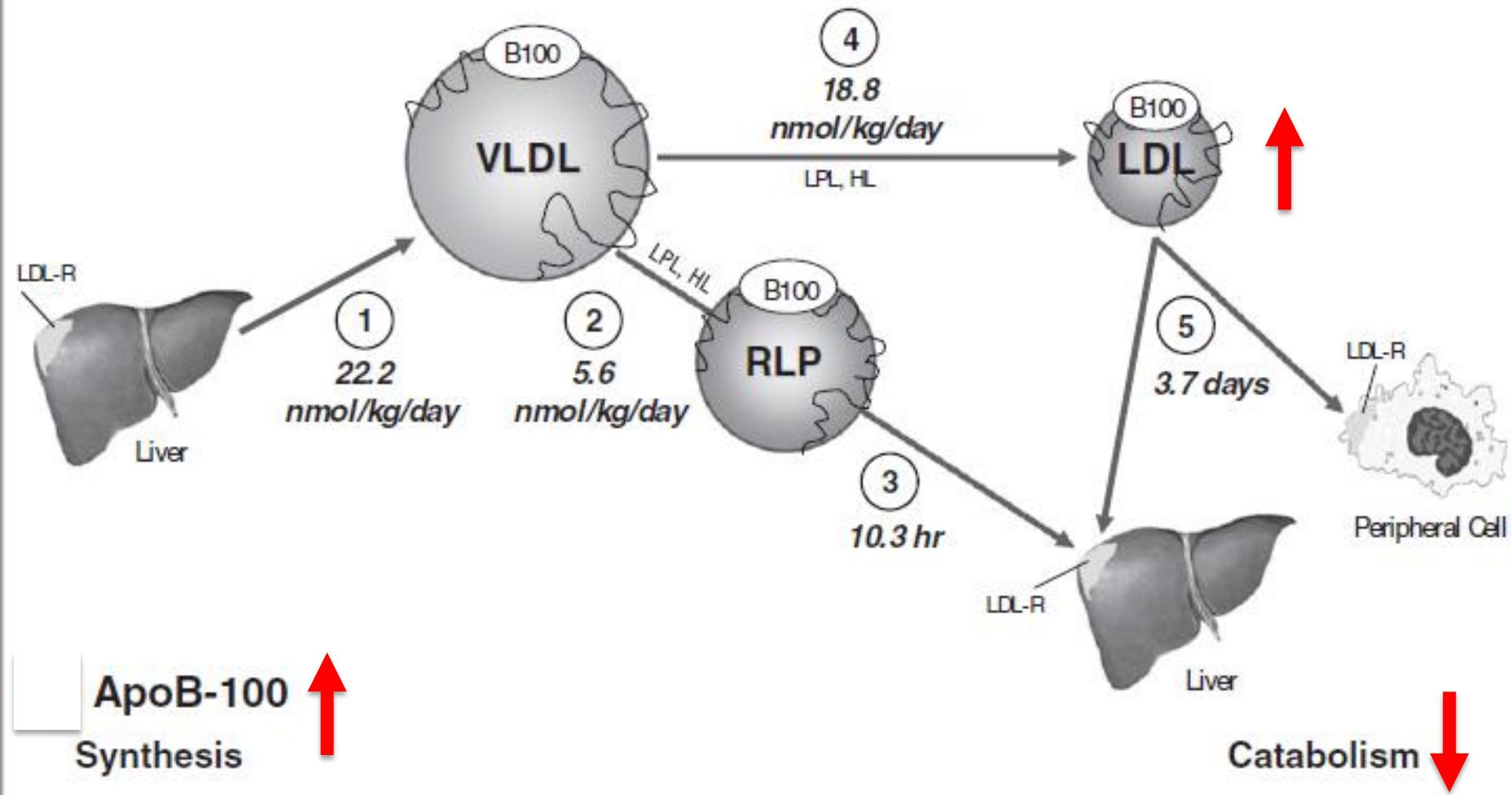


On the metabolic conversion of human plasma very low density lipoprotein to low density lipoprotein

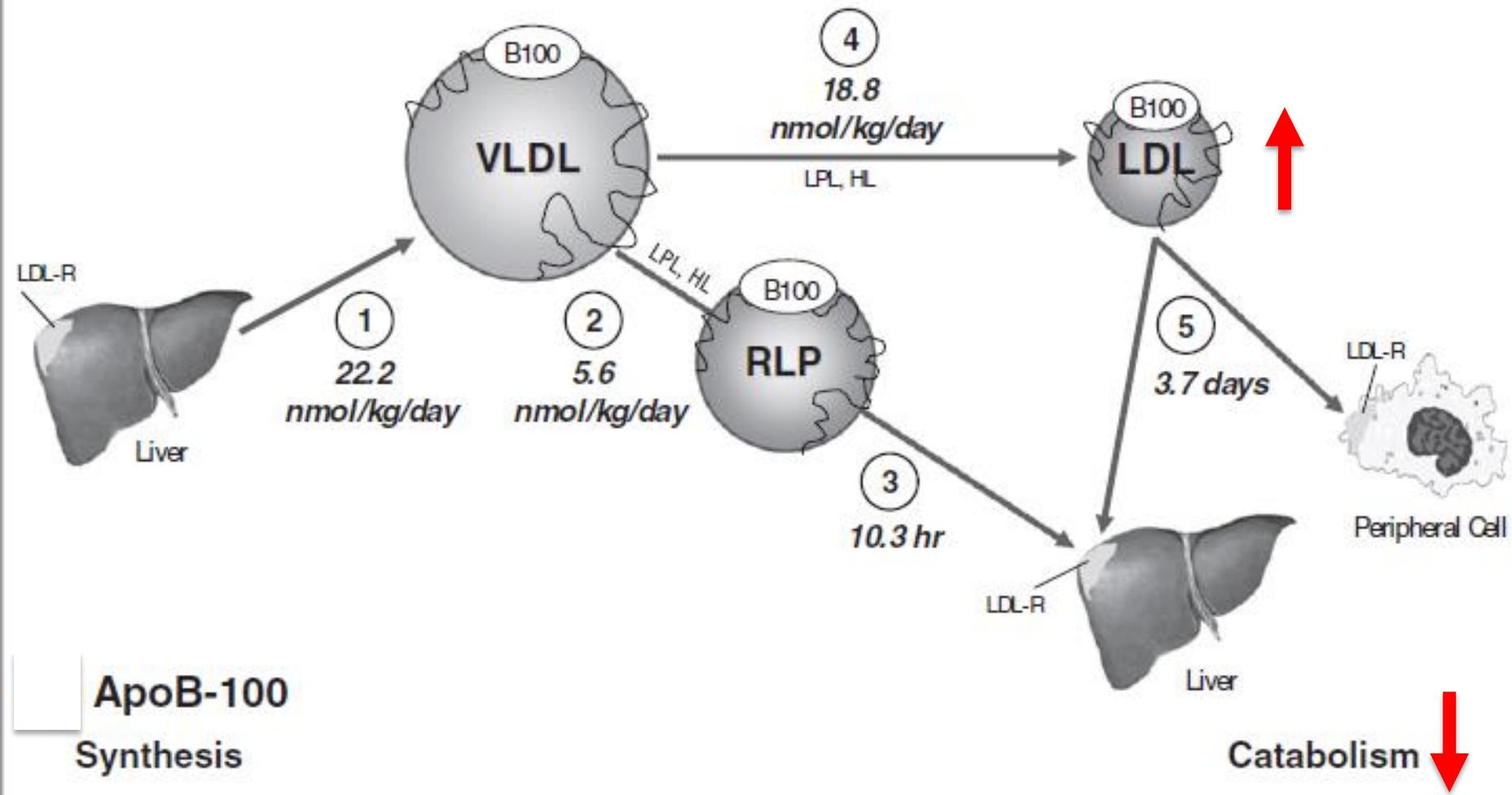
Eisenberg S, Bilheimer DW, Levy RI, Lindgren FT.



Model for the metabolism of apoB-100 in VLDL, IDL, and LDL



Model for the metabolism of apoB-100 in VLDL, IDL, and LDL



ApoB-100
Synthesis

Catabolism

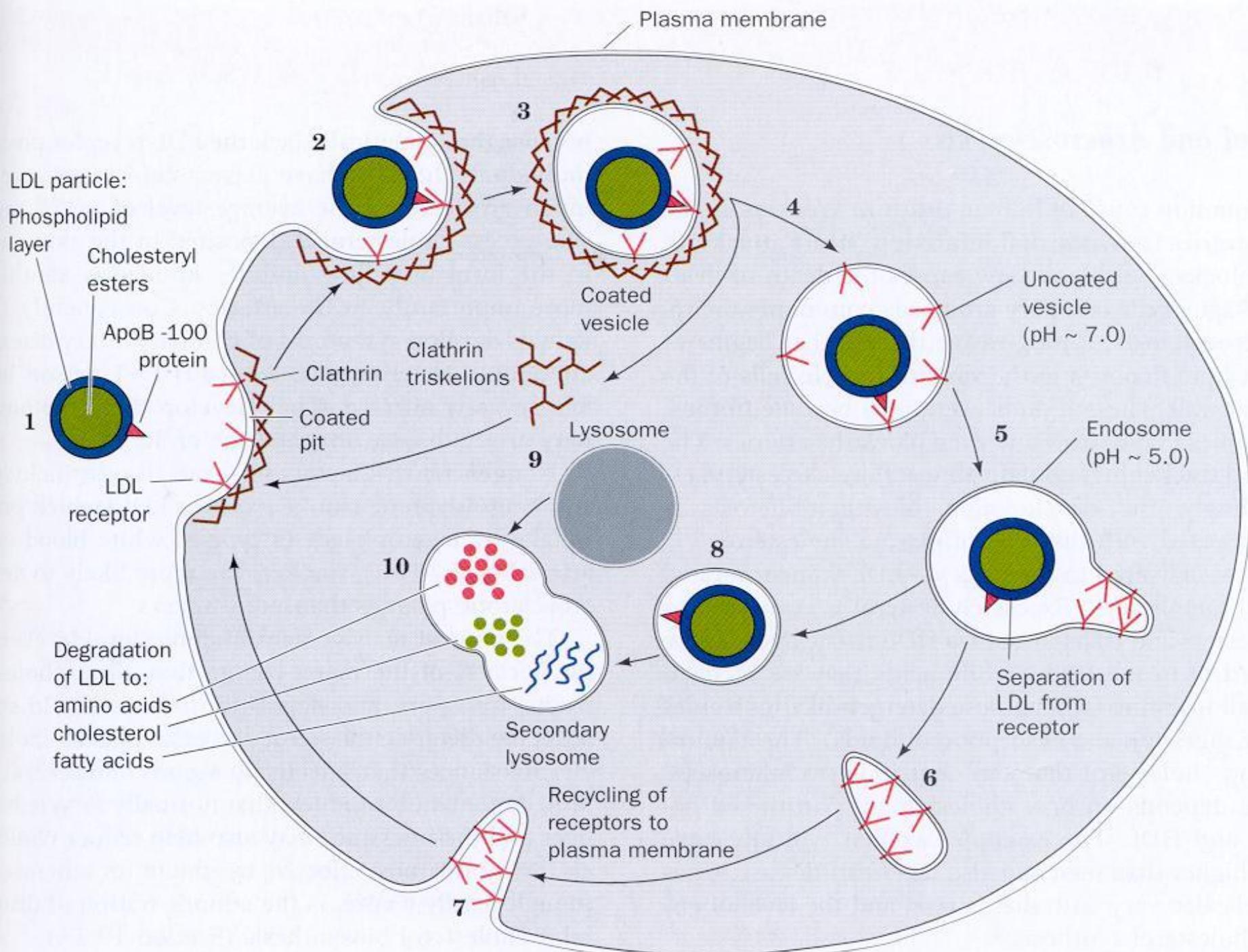
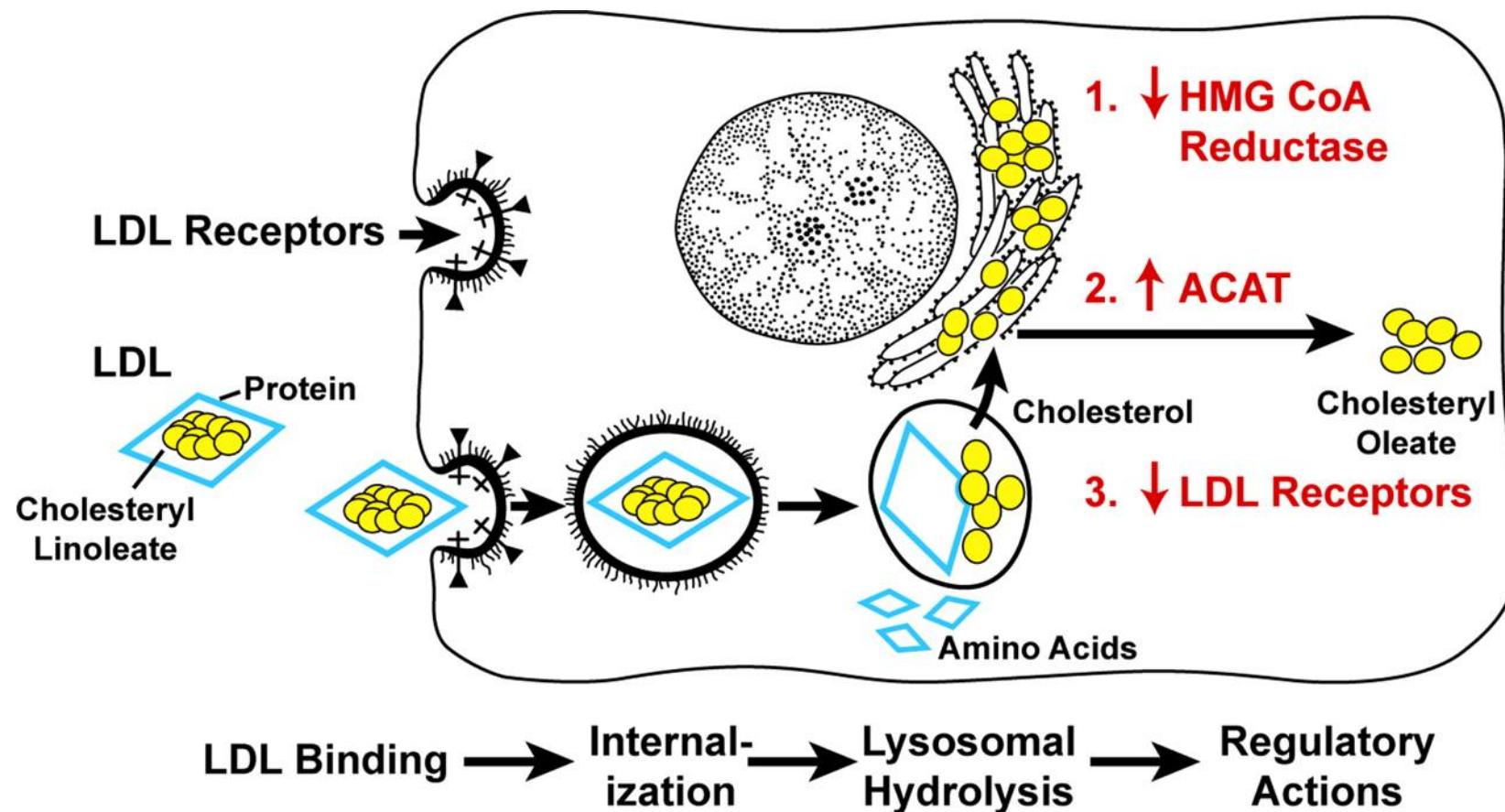


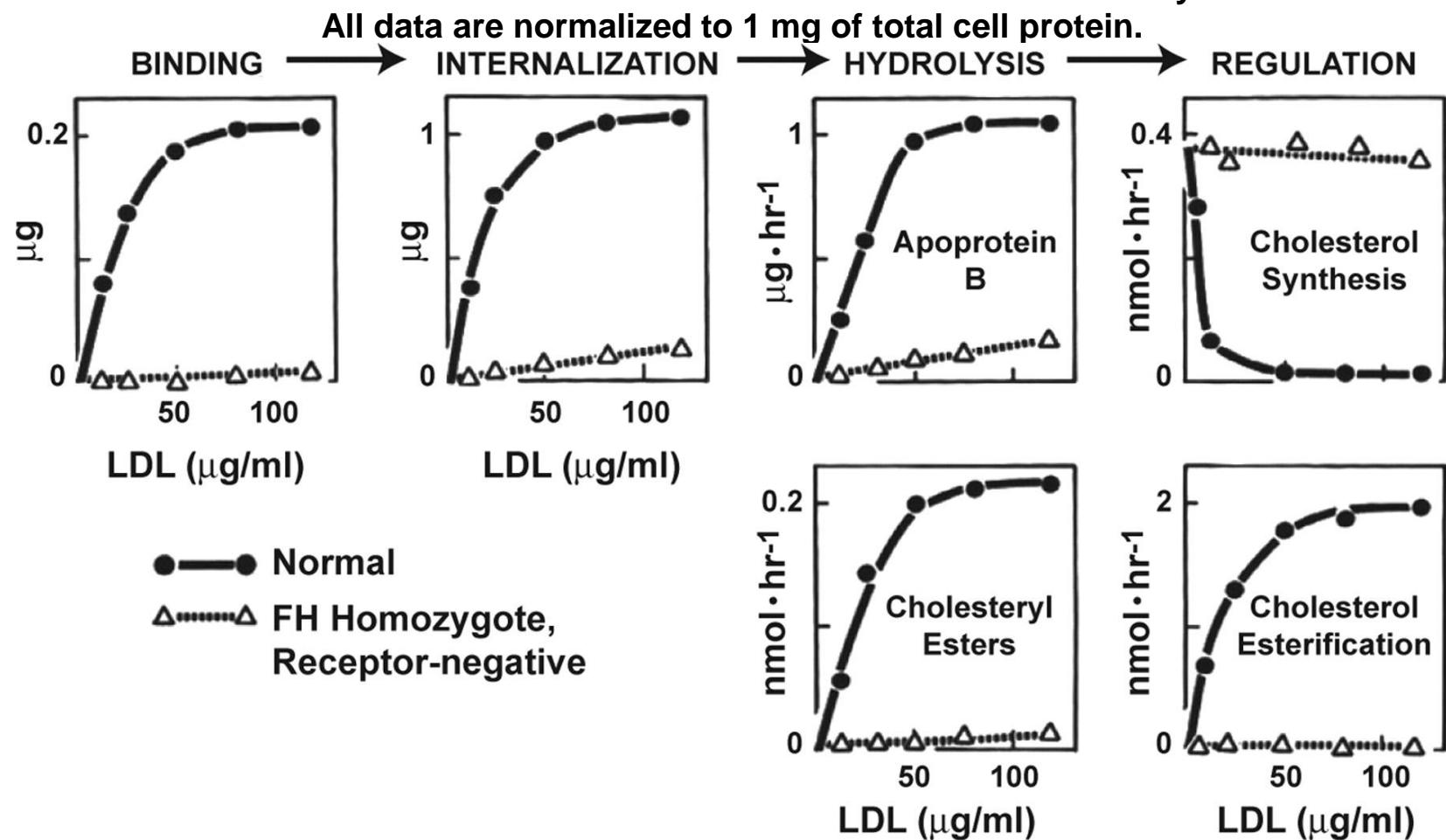
Figure 4. Sequential steps in the LDL receptor pathway of mammalian cells (already defined in text; modified from Brown and Goldstein58).

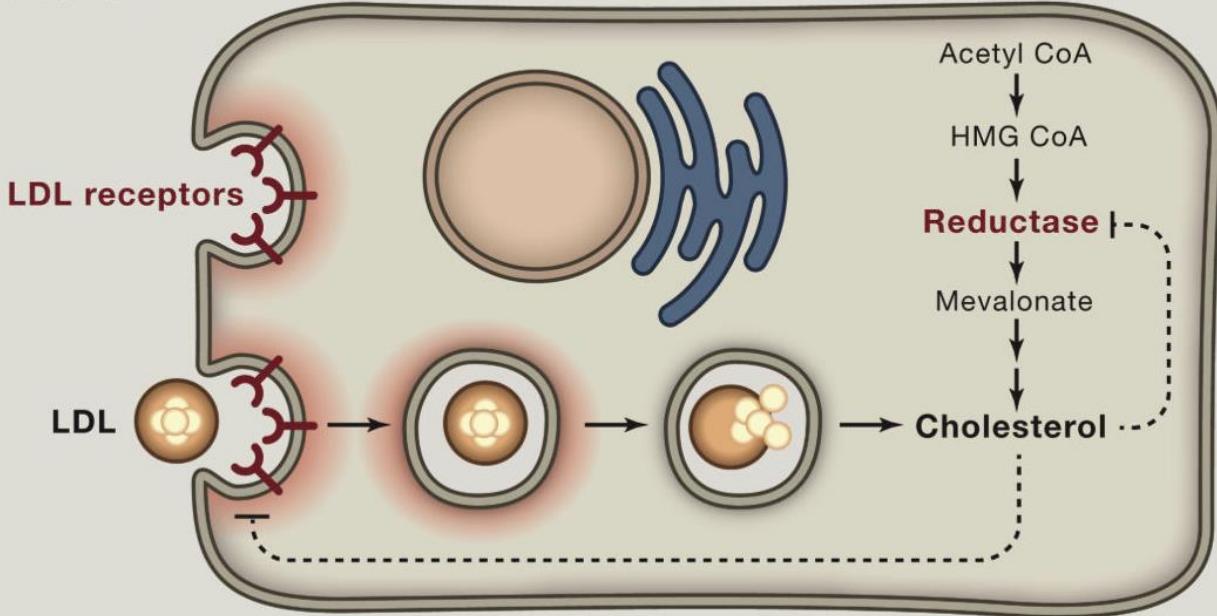


Joseph L. Goldstein, and Michael S. Brown Arterioscler
Thromb Vasc Biol. 2009;29:431-438

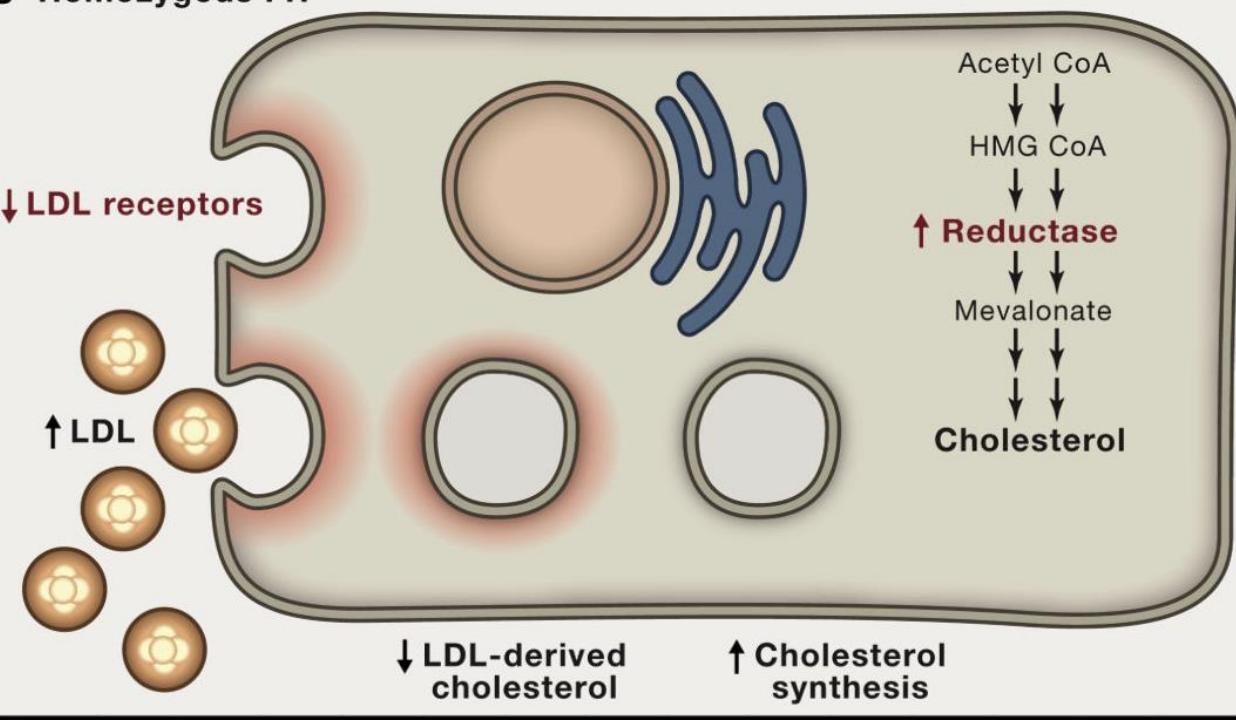


Figure 5. Actions attributable to the LDL receptor in fibroblasts from a normal subject and from a homozygote with the receptor-negative form of FH. Cells were incubated with varying concentrations of ^{125}I -LDL or unlabeled LDL at 37°C for 5 hours and assayed as described.⁵⁸



A Normal

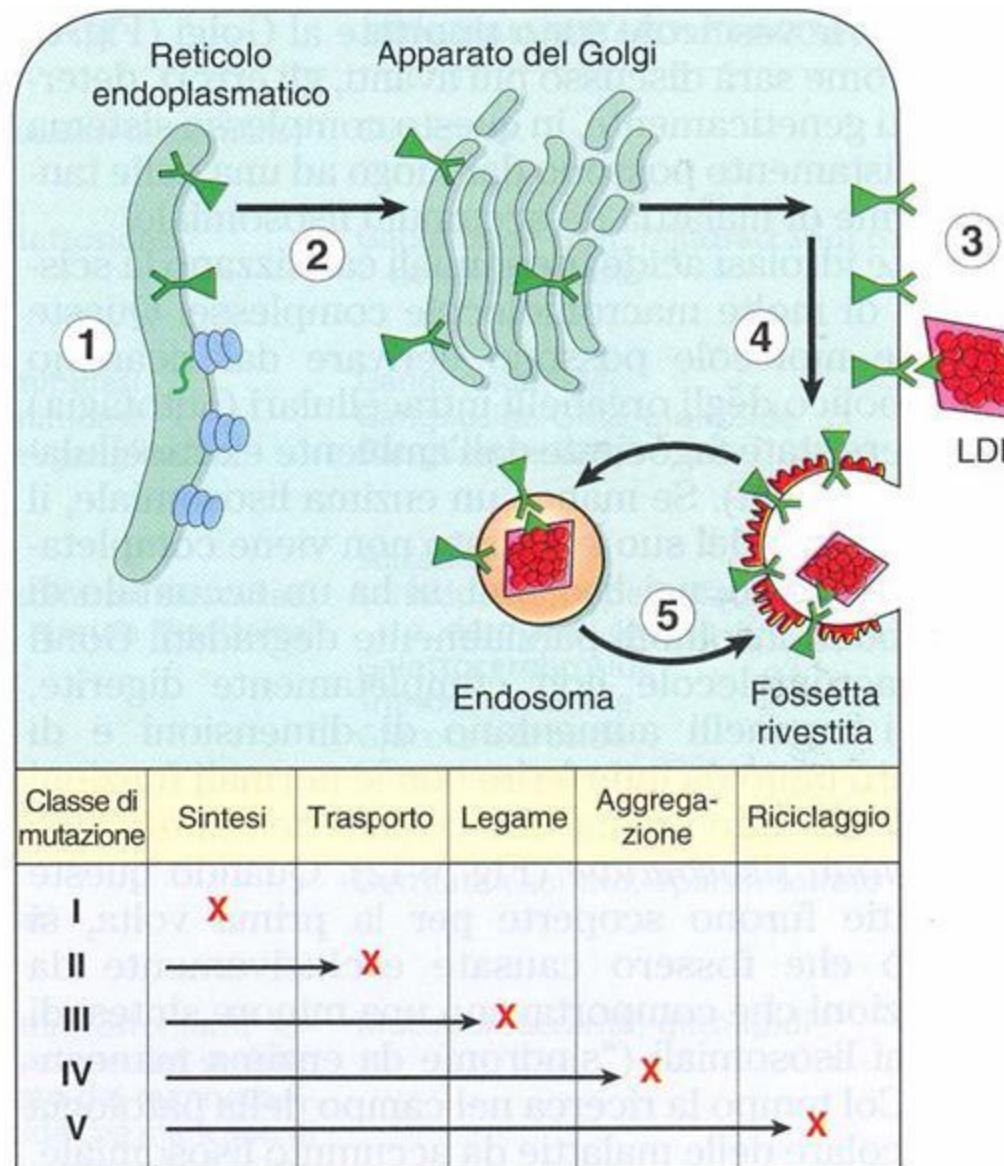
Feedback Regulation of Cholesterol Synthesis and LDL Receptors in Cultured Cells from **Normal Subjects** and **Children with Homozygous FH**

B Homozygous FH

Cell. 2015 March 26

Classi funzionali delle mutazioni dell'LDL-R

Le mutazioni del gene del recettore delle LDL appartengono a 5 classi funzionali, in relazione a quale stadio del ciclo intracellulare del recettore venga alterato o abolito



PCSK9 in the regulation of LDL receptor expression

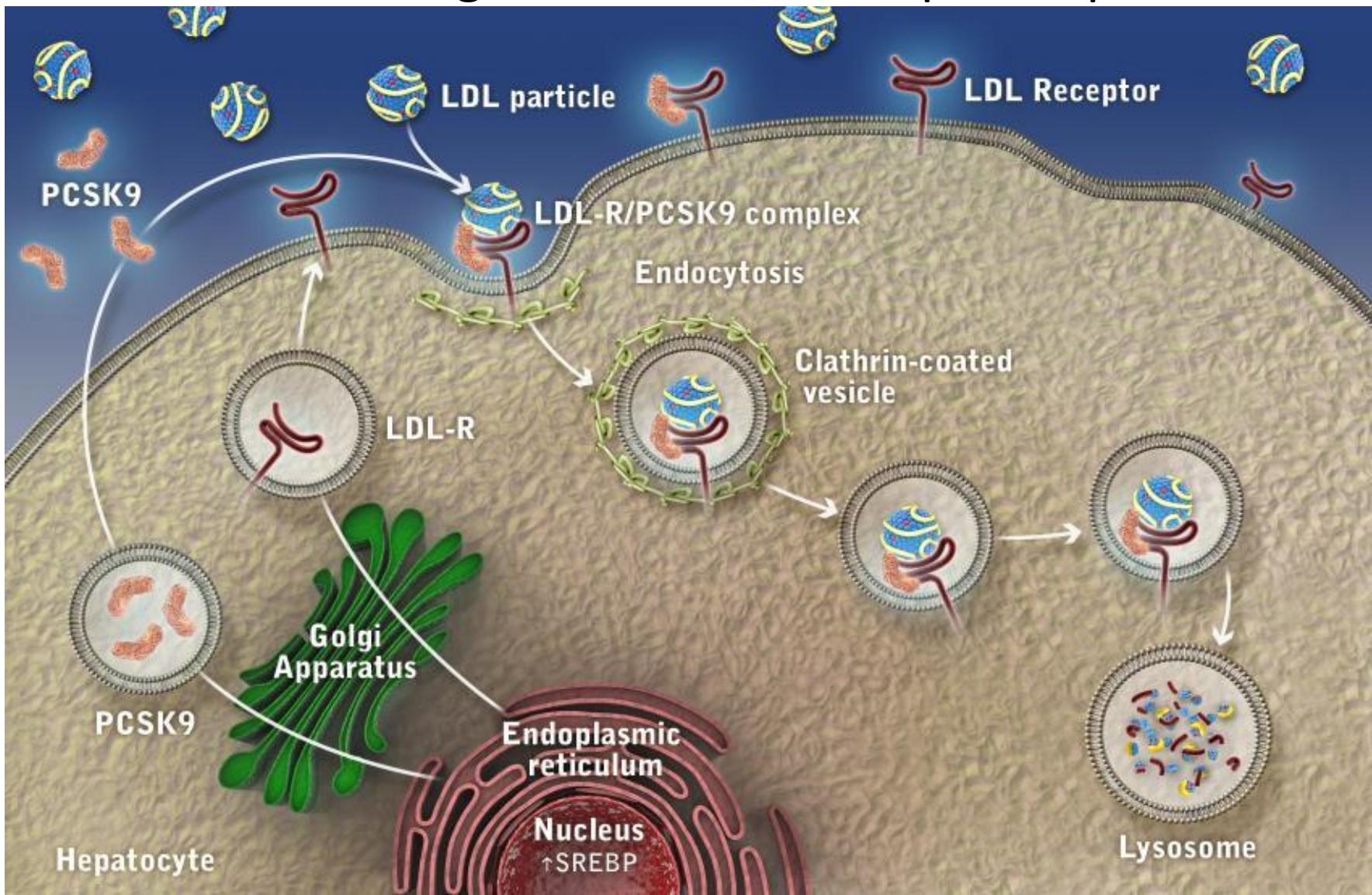


TABLE 1. Summary of the phenotypes of the available knockout mice for the convertases and their inhibitors

Convertases/inhibitors	Null gene approach	Null phenotype
Furin	Homologous recombination	Mice die at e10.5 due to hemodynamic insufficiency, ventral closure defect, axial rotation defect, abnormal yolk sac vasculature.
PC1	Homologous recombination	Mice viable, but 60% of normal size with defects in the processing of hormone precursors, hyperproinsulinemia. In humans: severe early obesity, adenocortical insufficiency, and hyperproinsulinemia.
PC2	Neomycin resistance gene	Mice viable, retarded growth, hypoglycemia, defects in the processing of endocrine peptides.
PACE4	Homologous recombination	Mice (25%) die at e10.5 due to situs defects and/or craniofacial malformations.
PC4	Homologous recombination	Mice viable with reduced fertility.
PC5	Homologous recombination	Mice die at e4.5–7.5.
PC7	Homologous recombination	No apparent abnormal phenotype.
SKI-1 (S1P)	Homologous recombination	Mice die at e4. Disruption of S1P prevents normal epiblast formation and subsequent implantation.
	Inducible Cre recombinase (liver)	Mice with reduced cholesterol and fatty acid synthesis.
PCSK9 (NARC-1)	Homologous recombination	Enhanced cholesterol uptake by the liver. In humans: Mutation-induced gain of function: hypercholesterolemia (autosomal dominant hypercholesterolemia). Mutation-induced loss of function: hypocholesterolemia.
7B2	Transposon-based approach	Mice die 9 wk after birth from Cushing's disease due to ACTH hypersecretion.
ProSaas	Not available	Not available

Table 1. Phenotypic comparison of wild-type and *Pcsk9*^{-/-} mice

Parameter	WT	<i>Pcsk9</i> ^{-/-}
No. of mice	4	4
Body weight, g	25.5 ± 0.6	30.0 ± 1.6
Liver cholesterol, mg/g	2.20 ± 0.16	2.00 ± 0.02
Liver TG, mg/g	9.2 ± 0.6	7.2 ± 0.7
Plasma cholesterol, mg/dl	95.7 ± 9.4	46.3 ± 1.9*
Plasma TG, mg/dl	70.0 ± 11	85.8 ± 7.5

Knockout mice lacking PCSK9



Statin administration produced:

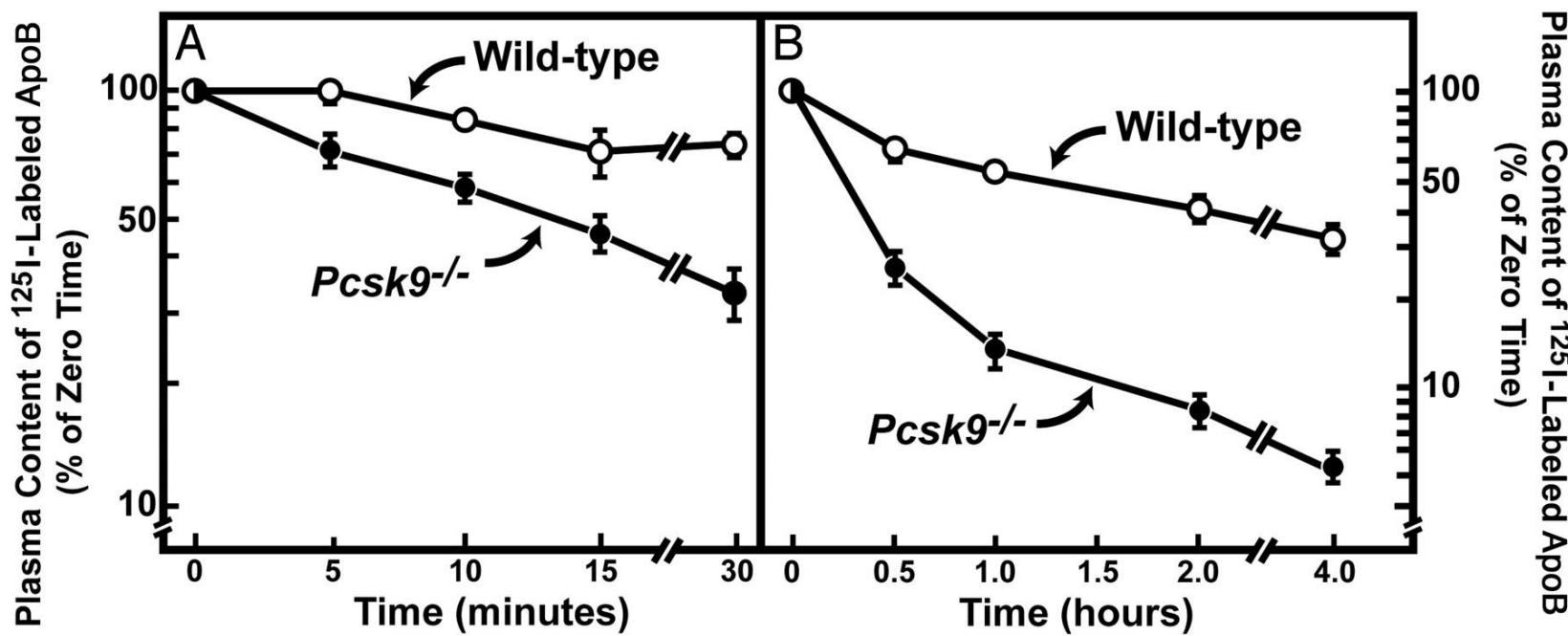
- an exaggerated increase in LDL receptor number in liver
- an enhanced LDL clearance from plasma

Rashid S. et al. PNAS 2005

Among FH-1 heterozygous patients with a good response to statin therapy, 8.8% were carriers of loss of function mutation of PCSK9 gene.

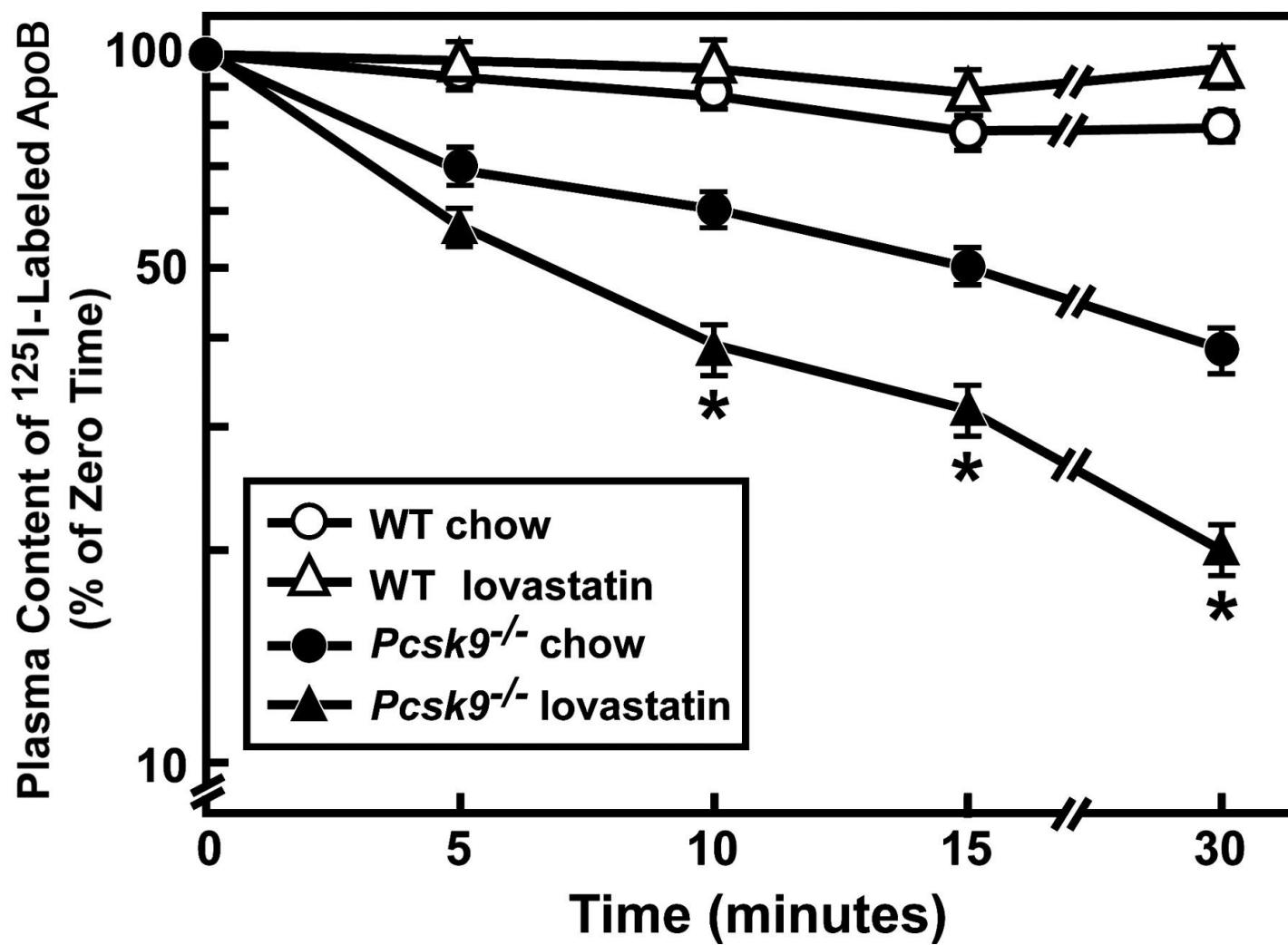
Berge KE. et al. ATVB 2006

Plasma clearance of ^{125}I -labeled mouse LDL in WT and $\text{Pcsk9}^{-/-}$ mice.



Rashid S et al. PNAS 2005;102:5374-5379

Plasma clearance of ^{125}I -labeled mouse LDL in WT and $\text{Pcsk9}^{-/-}$ mice fed chow or lovastatin.



Rashid S et al. PNAS 2005;102:5374-5379

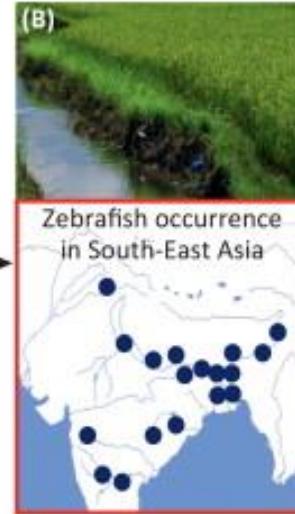
What is a zebrafish?

- *Danio rerio*
- Small freshwater fish from South Asia.
- 4 cm long when fully grown.
- Common aquarium fish.
- Very easy to look after.



Image: Wikimedia commons/Marribio2

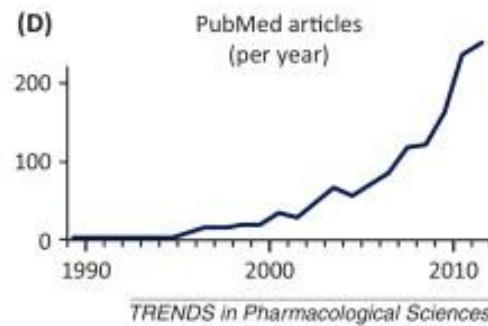
(A) Major zebrafish research centers worldwide

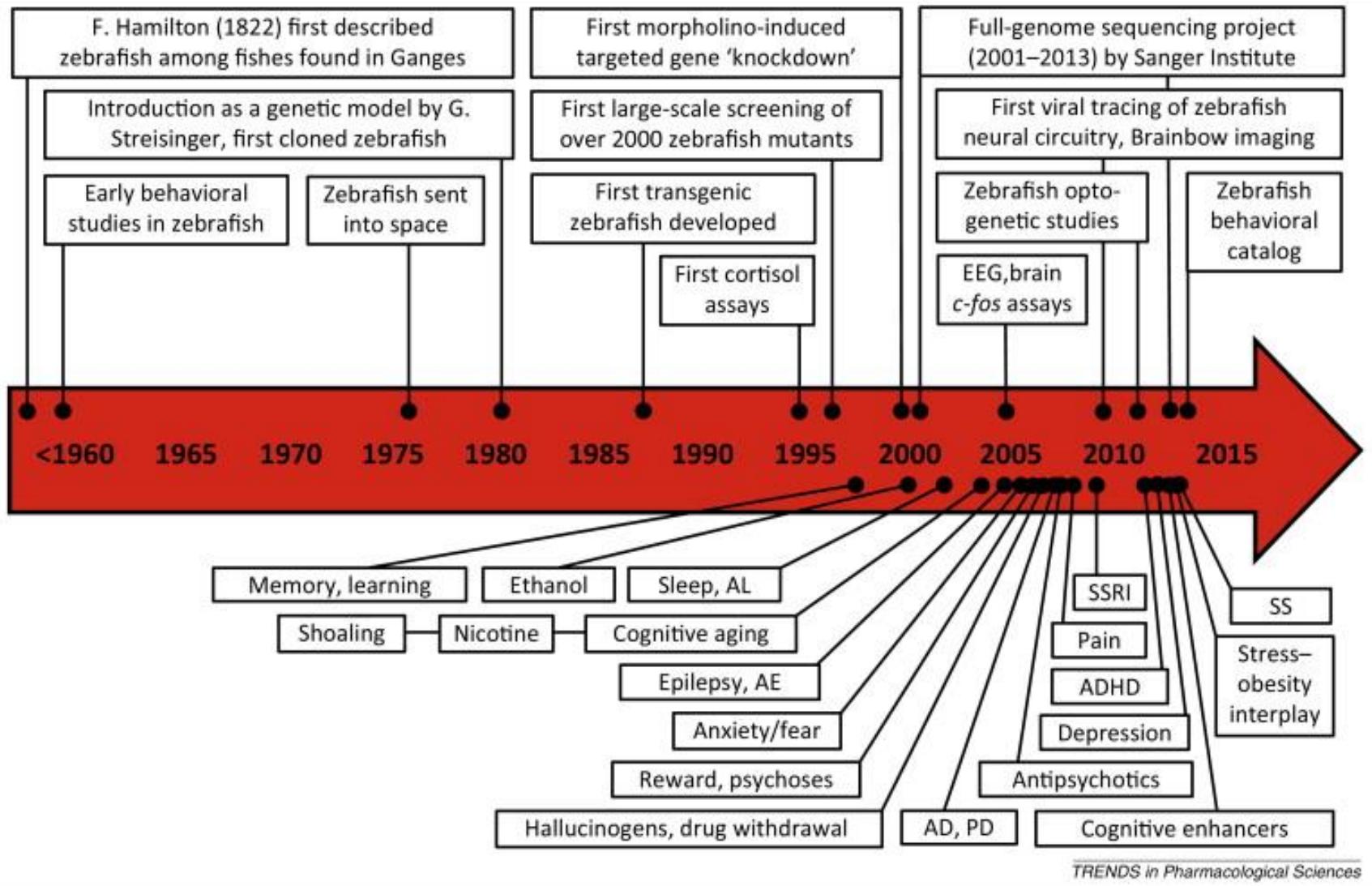


(C)



(D)





The timeline of the developing utility of zebrafish models in neuroscience and neuropharmacology research

Why use zebrafish?

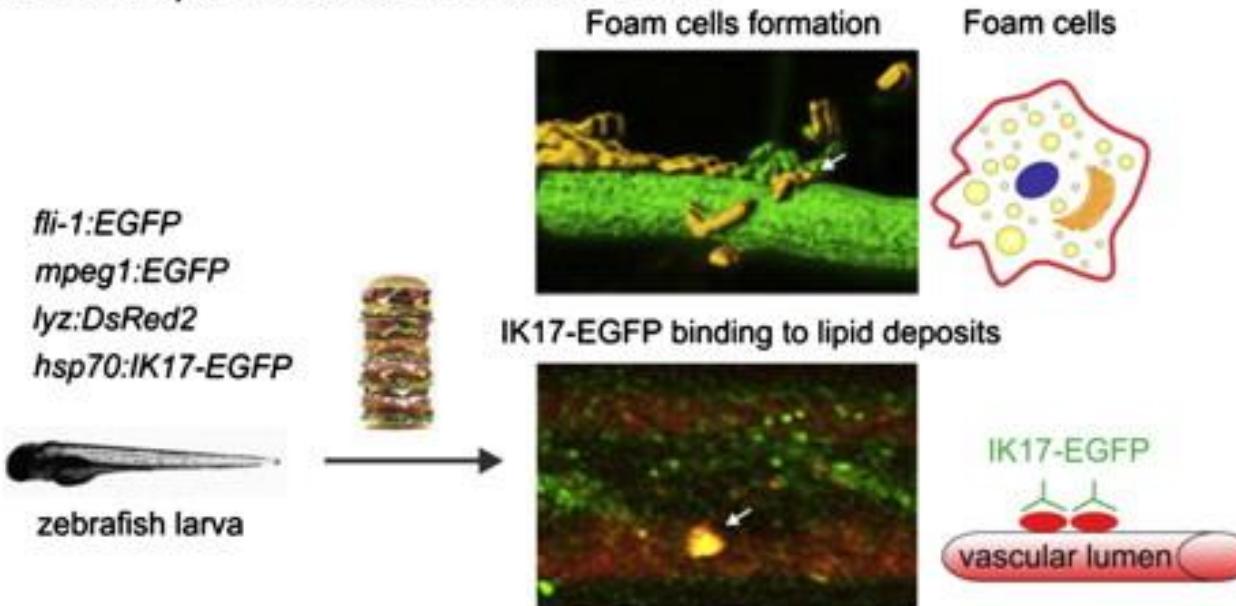
- Small size.
- All major organs present within 5 days post fertilisation.
- Short generation time (3-4 months).
- Produces 300-400 eggs every 2 weeks.
- Translucent embryos.
- Lots of genome resources available.



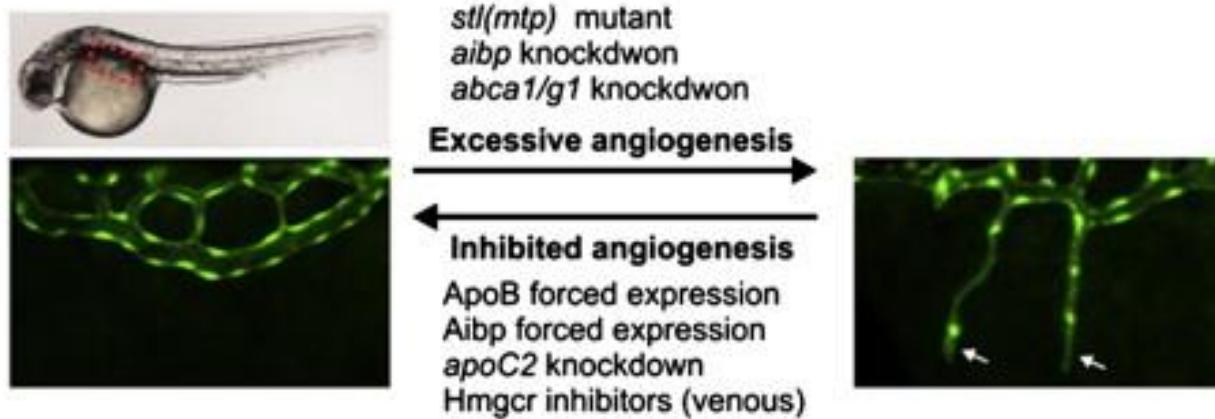
Image: TBC

A

Vascular lipid accumulation & oxidation

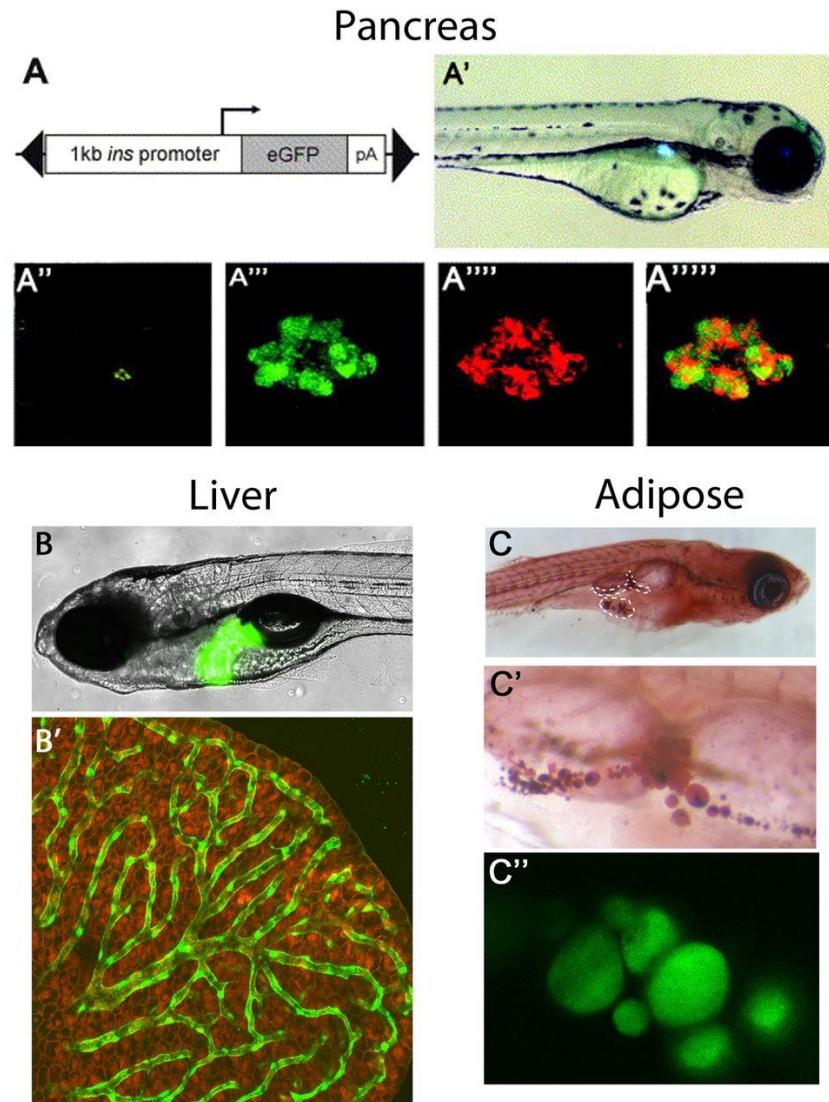
**B**

Dysregulated angiogenesis



Zebrafish models to study mechanisms relevant to atherosclerosis (A) and angiogenesis (B).

Visualisation of metabolic tissues in zebrafish.

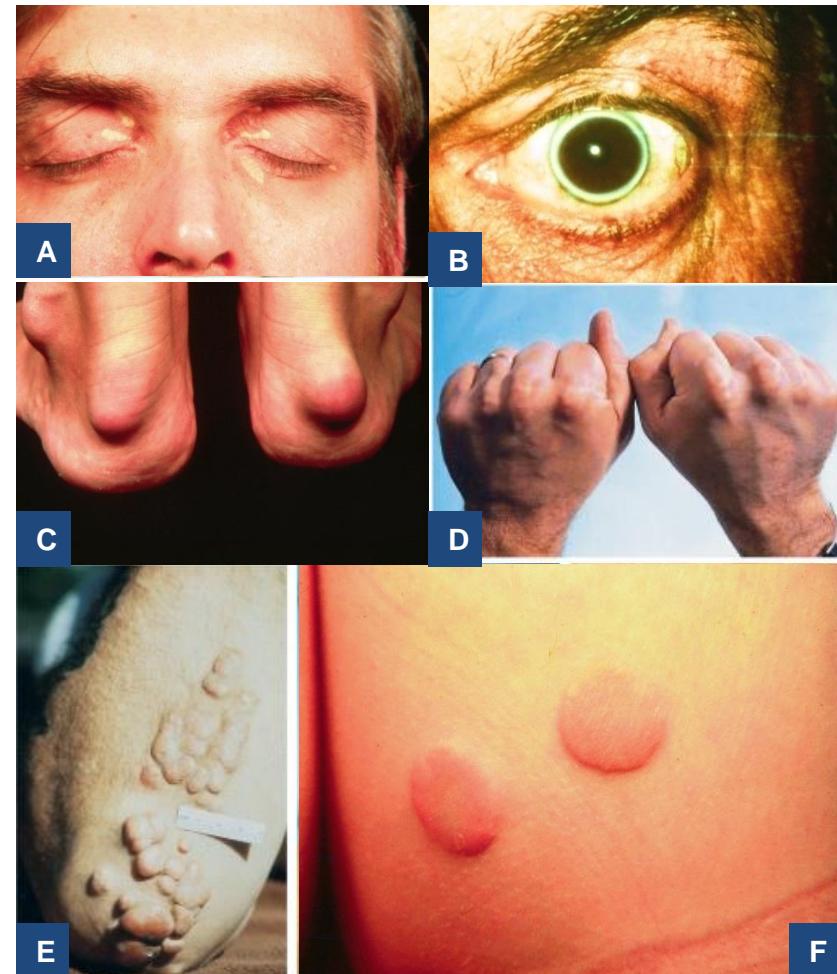


The clinical diagnosis

When to make a clinical suspicion

- Total plasma cholesterol in adults ≥ 310 (290) mg/dL
- Total plasma cholesterol in children ≥ 260 mg/dL
- Premature CHD
- Tendon Xantomas
- Family history of premature CHD
- Family history of sudden cardiac death

- A. Xanthelasma
- B. Corneal arcus^a
- C. Achilles tendon xanthomas
- D. Tendon xanthomas^{b,1-3}
- E. Tuberous xanthomas^c
- F. Planar xanthomas^c



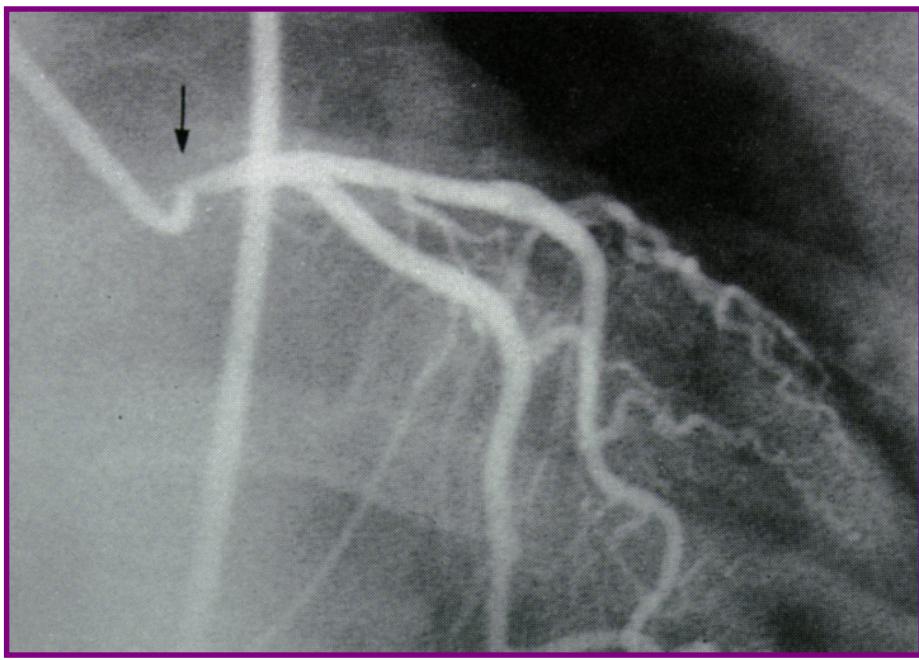
^a Common in older individuals (even non-FH); definitive of FH in younger individuals.

^b 30%-50% of the HeFH population have tendon xanthomas.

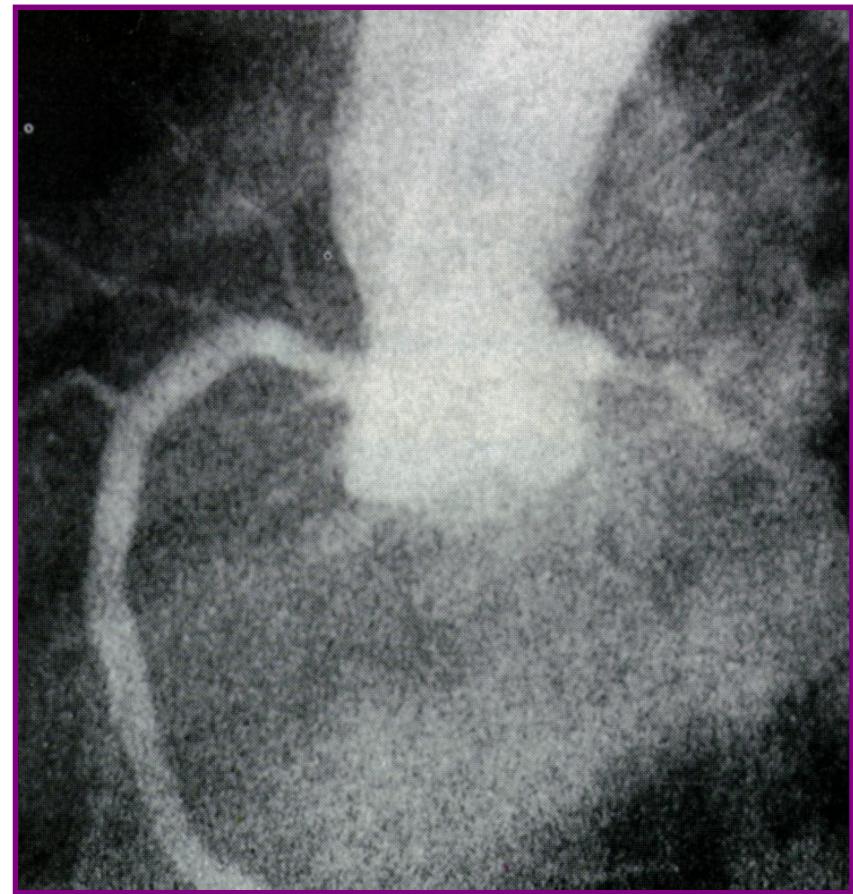
^c Seen mostly in HoFH, and not as often in HeFH

1. Ferrières J, et al. *Circulation*. 1995;92(3):290-295.
2. Bertolini S, et al. *Arterioscler Thromb Vasc Biol*. 2000;20(9):E41-E52.
3. Descamps OS, et al. *Atherosclerosis*. 2001;157(2):514-518.

Figure adapted from Mahley RW, et al. In: Kronenberg HM. *Williams Textbook of Endocrinology*. 11th ed. Philadelphia: Saunders; 2008.



Stenosi della a. coronaria sx



Depositi lipidici sopravalvolari della semilunare aortica

CRITERI DIAGNOSTICI PER L'IPERCOLESTEROLMIA FAMILIARE

Table 1. Summary diagnostic criteria for familial hypercholesterolaemia

Criteria	Dutch	Simon Broome	MEDPED	Japan
Family History premature CVD	+	+		+
Family History tendon xanthoma	+	+		
Patient premature CVD	+			
Patient premature PVD	+			
Tendon Xanthoma	+	+		+
Arcus cornealis	+			
Cholesterol	+	+	+	+
Family History Cholesterol		+	+	+

Feature

Score

DUTCH FH CRITERIA**Family history**

First-degree relative with known premature coronary and/or vascular disease
(men <55 years, females <60 years)
OR First-degree relative with known LDL-C above the 95th percentile for age and sex

1

First-degree relative with tendinous xanthomata and/or arcus cornealis
OR Children aged less than 18 years with LDL-C above the 95th percentile
for age and sex

2

Clinical history

Premature coronary artery disease (men <55 years, females < 60 years)

2

Premature cerebral or peripheral vascular disease (men <55 years,
females <60 years)

1

Physical examination

Tendinous xanthomata

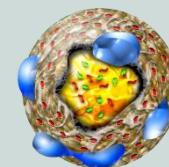
6

Arcus cornealis prior to age 45 years

4

LDL-C (mmol/L)

- 8.5 or higher
- 6.5 to 8.4
- 5.0 to 6.4
- 4.0 to 4.9



8

5

3

1

DNA analysis: functional mutation in the *LDLR*, *APOB* or *PCSK9* gene

8

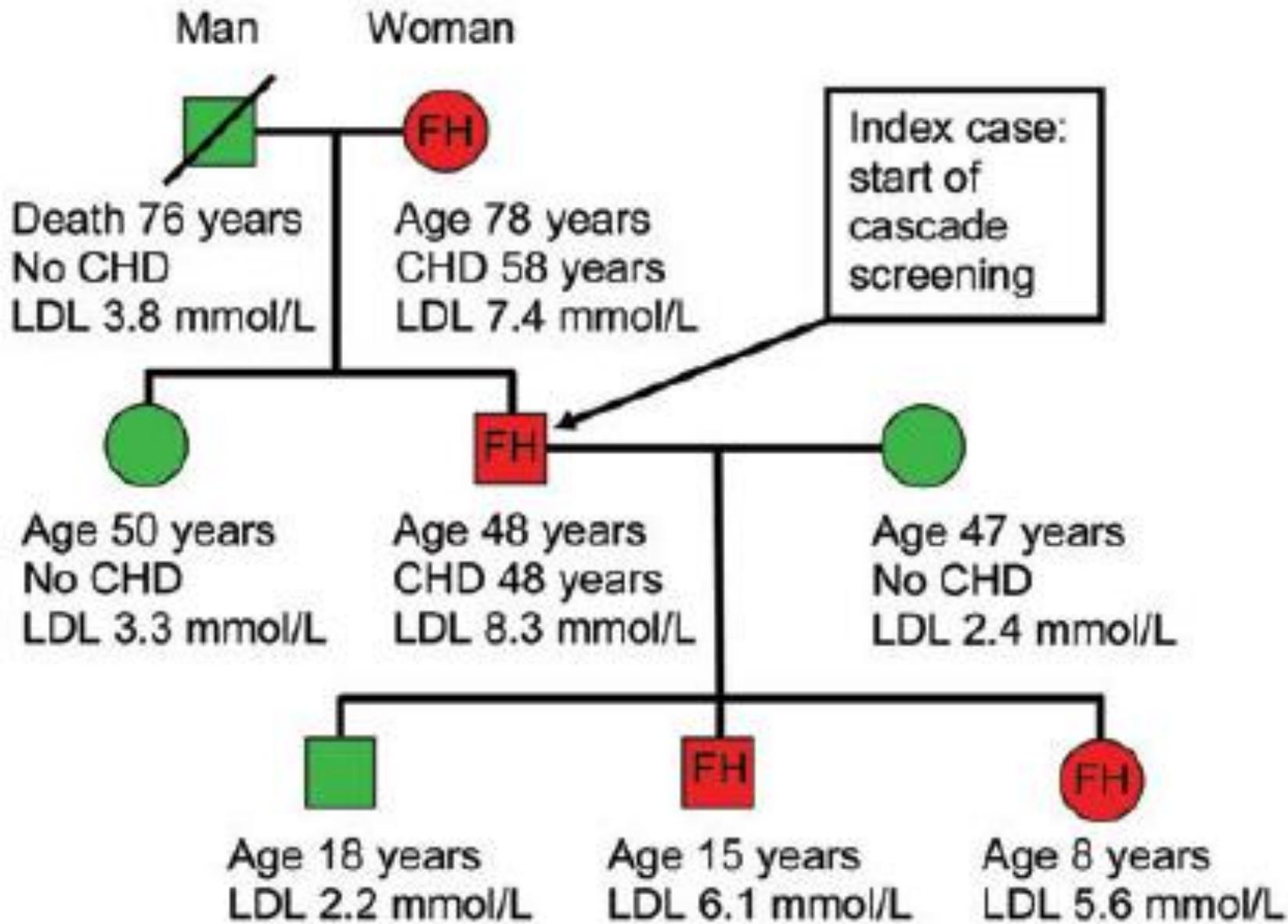
Stratification of familial hypercholesterolaemia (FH), as determined by total score using the Dutch Lipid Clinic Network Criteria:

- Definite FH = total score greater than 8
- Probable FH = total score between 6 and 8
- Possible FH = total score between 3 and 5
- Unlikely FH = total score of less than 3

DLCN CRITERIA: Probabilities to be FH

- Definite FH score > 8p
- Probable FH score 6 – 8p
- Possible FH score 3 – 5p
- Unlikely FH score < 3p

Cascade Screening



Lipid Goals and recommandations to treat severe hypercholesterolemias

LDL cholesterol goals:
(heterozygous & homozygous FH)

- $<3.5\text{mmol/L}(<135\text{mg/dL})$ for children
- $<2.5\text{mmol/L}(<100\text{mg/dL})$ for adults
- $<1.8\text{mmol/L}(<70\text{mg/dL})$ for adults with known CHD or diabetes

In addition to lifestyle and dietary counselling, treatment priorities are

Children (from age 8-10):

1. Statin
2. Ezetimibe
3. Bile acid binding resin
4. Lipoprotein apheresis in homozygotes

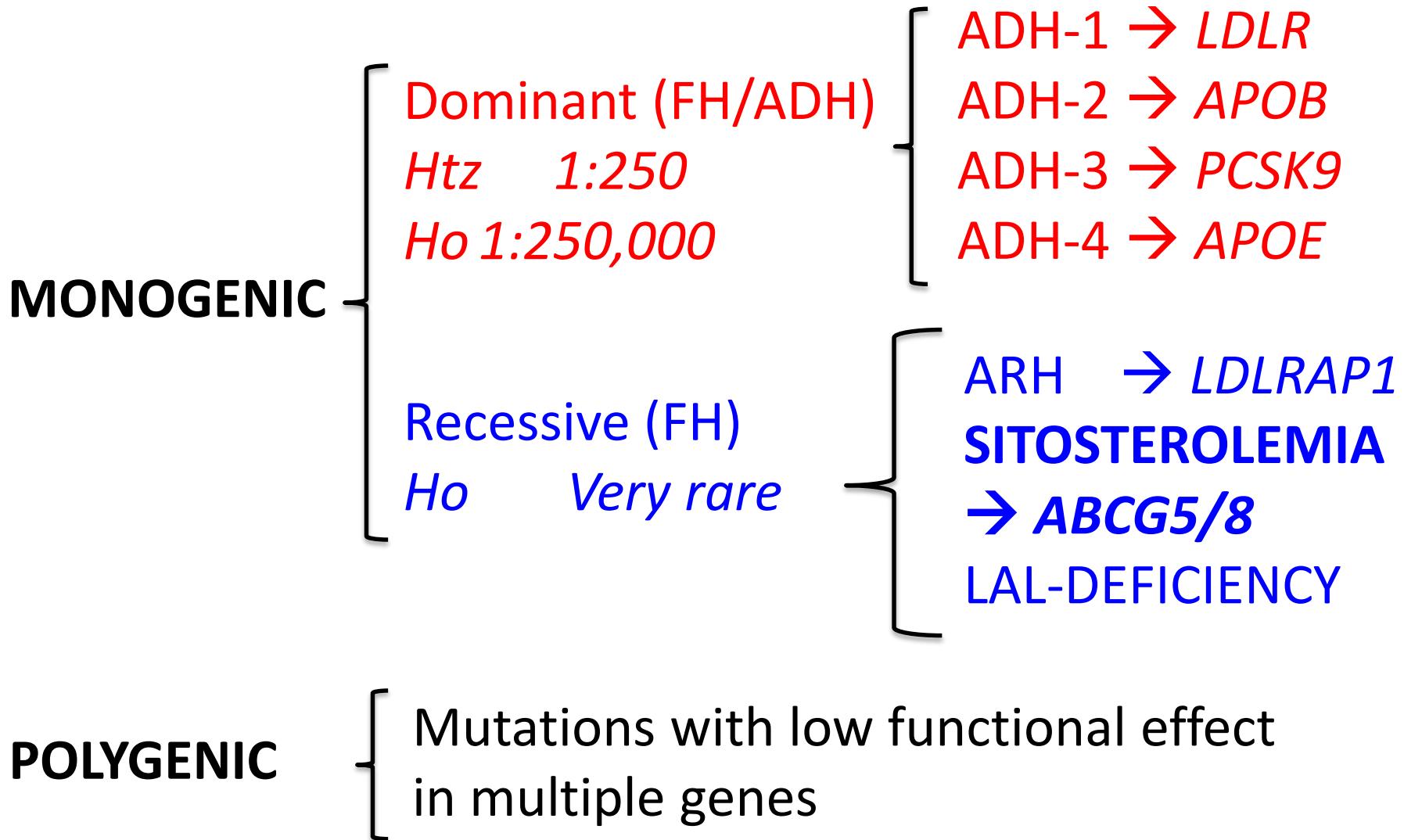
Adults:

1. Maximal potent statin dose
2. Ezetimibe
3. Bile acid binding resins
4. Lipoprotein apheresis in homozygotes & treatment-resistant heterozygotes with CHD

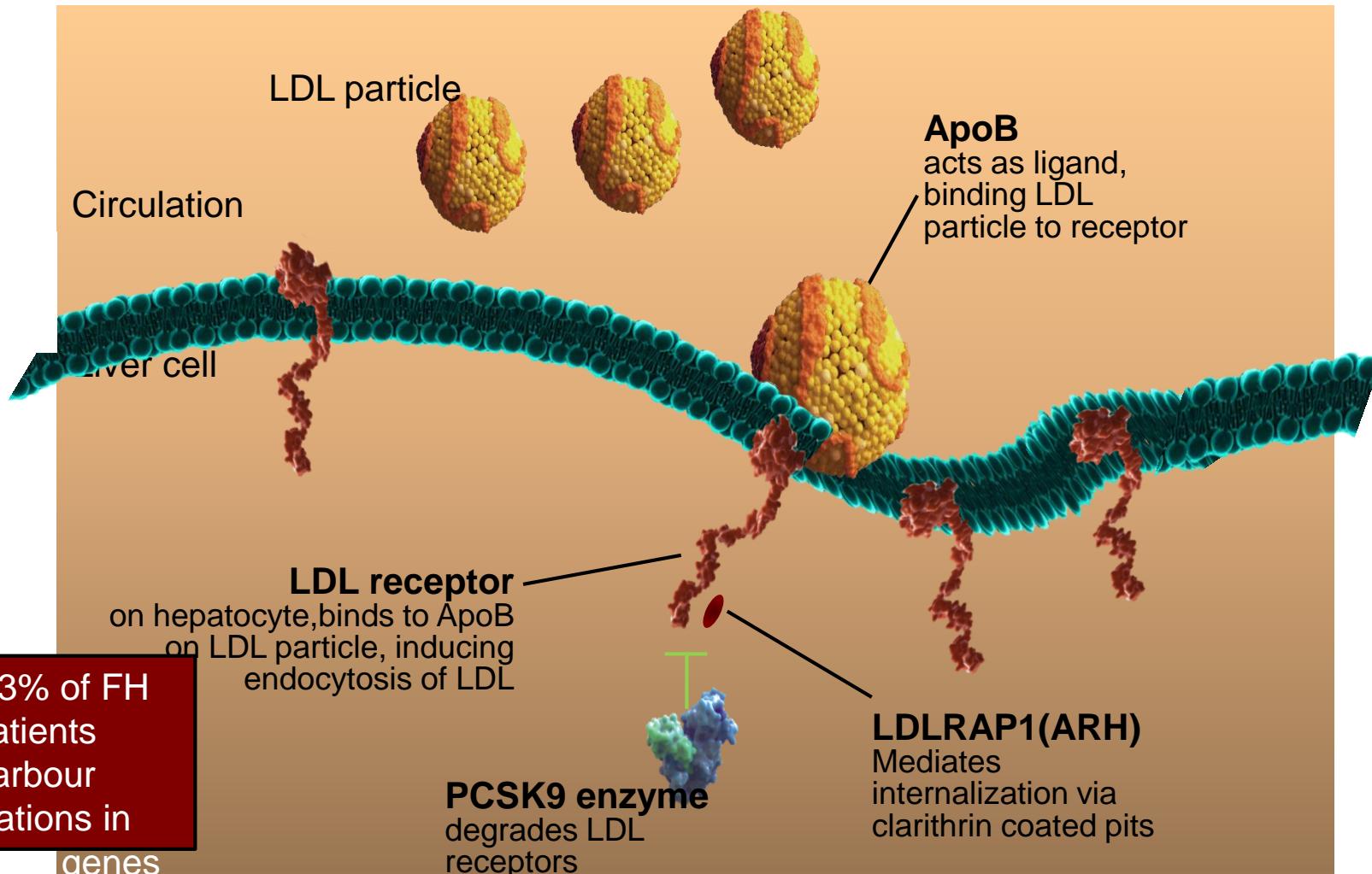
Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

Il laboratorio di biologia molecolare

PRIMARY HYPERCHOLESTEROLEMIAS [↑ LDL-C]



Familial hypercholesterolemia can be caused by mutations in 4 known genes



ApoB, apolipoprotein B; FH, familial hypercholesterolemia; GoF, gain of function; LDL, low-density lipoprotein; LDLRAP1, low-density lipoprotein receptor adapter protein 1; PCSK9, proprotein convertase subtilisin/kexin type 9.
De Castro-Oros I, et al. Appl Clin Genet 2010;3:53–64.

AMGEN®

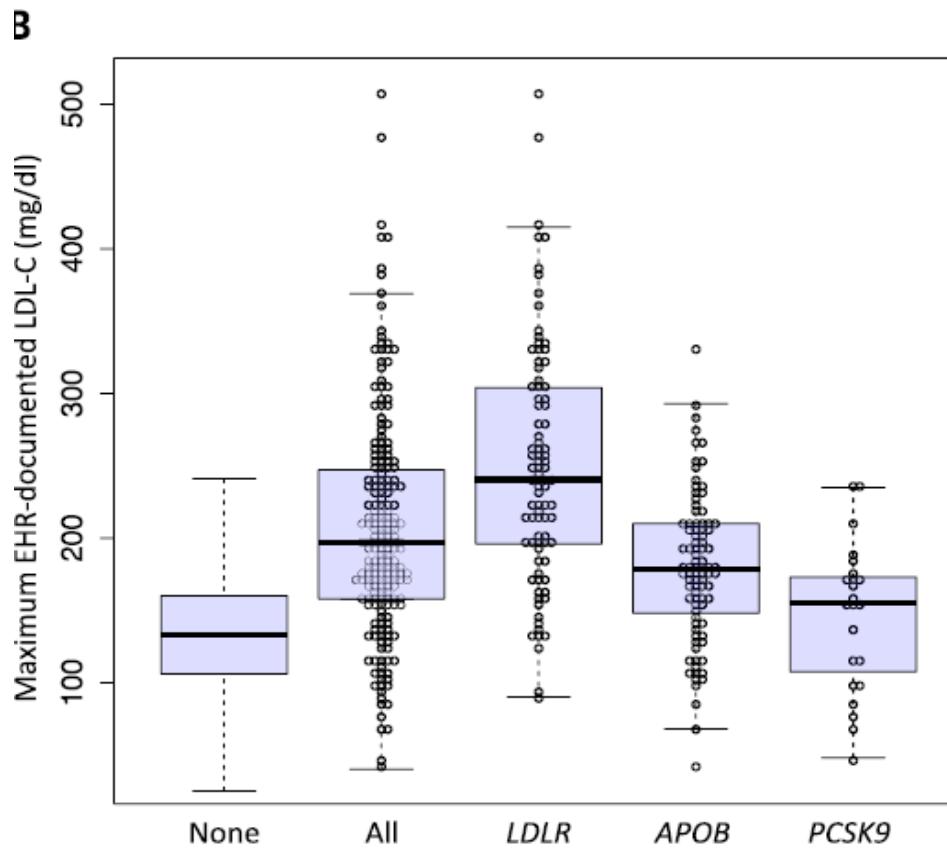
Cardiovascular



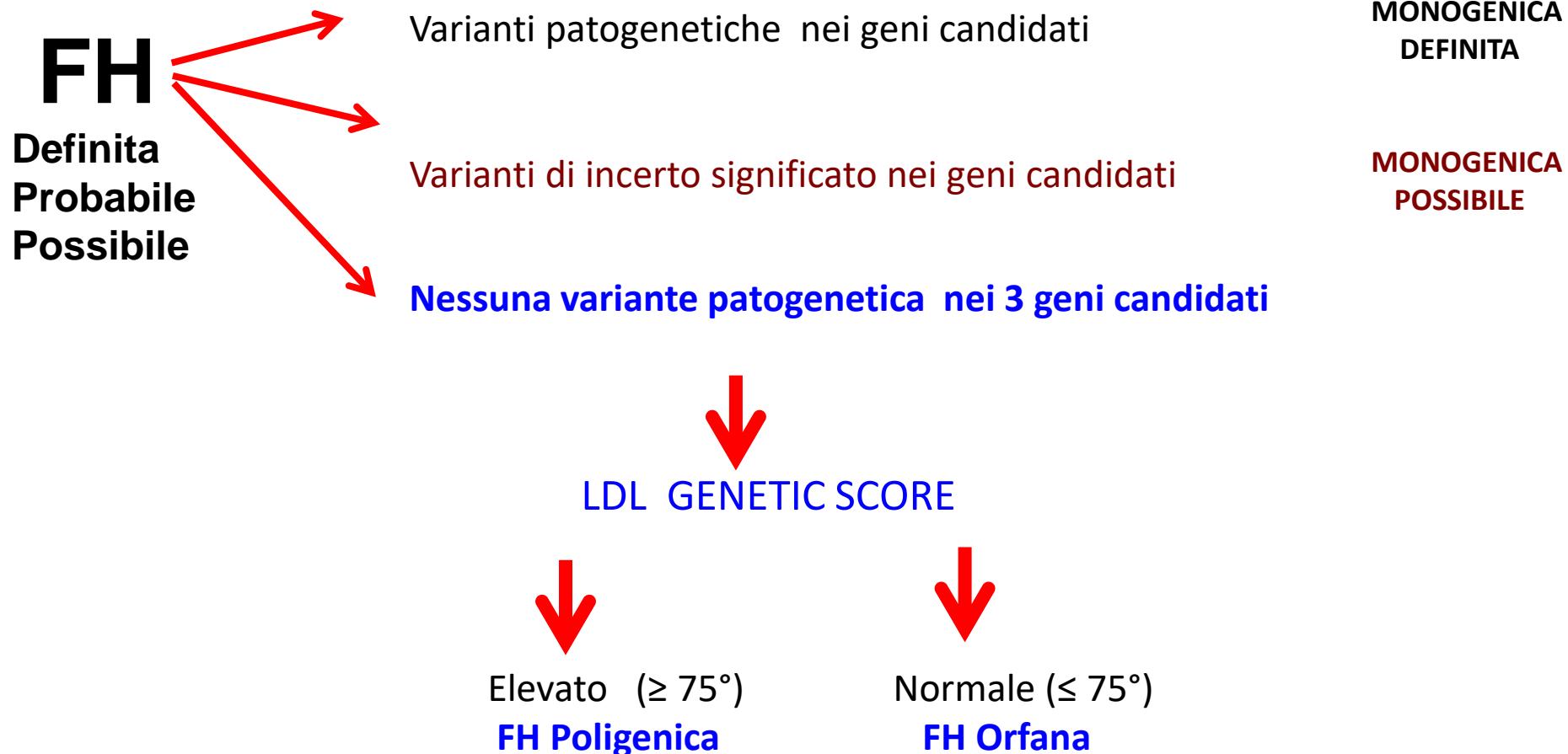
DISTRIBUTION OF PATHOGENIC VARIANTS IN FH CANDIDATE GENES

FH CANDIDATE GENES	HOLLAND	FRANCE	SPAIN	ITALY
LDLR (FH-1)	87.6 %	91.1 %	96.4 %	97.4 %
APOB (FH-2)	12.3 %	8.1 %	3.5 %	2.2 %
PCSK9 (FH-3)	0.1 %	0.8 %	0.1 %	0.4 %

LIVELLI MASSIMI DI LDL-C NEI PORTATORI DI VARIANTI PATOGENETICHE NEI GENI FH



Analisi genetica



LA FORMA POLIGENICA DI FH

VARIANTI GENICHE COMUNI AD EFFETTO INCREMENTALE SUI LIVELLI DI LDL-C

GENI COINVOLTI

APOE
LDLR
CELSR2
APOB
ABCG5/8
HFE
PCSK9
ST3GAL4
MYLIN
NYNRIN
SLC22A1

VARIANTI COMUNI IN QUESTI GENI CONCORRONO AD AUMENTARE IL LIVELLO DI LDL

MAGGIORE IL LORO NUMERO IN UN SINGOLO INDIVIDUO
(NUMBER OF RISK ALLELES)

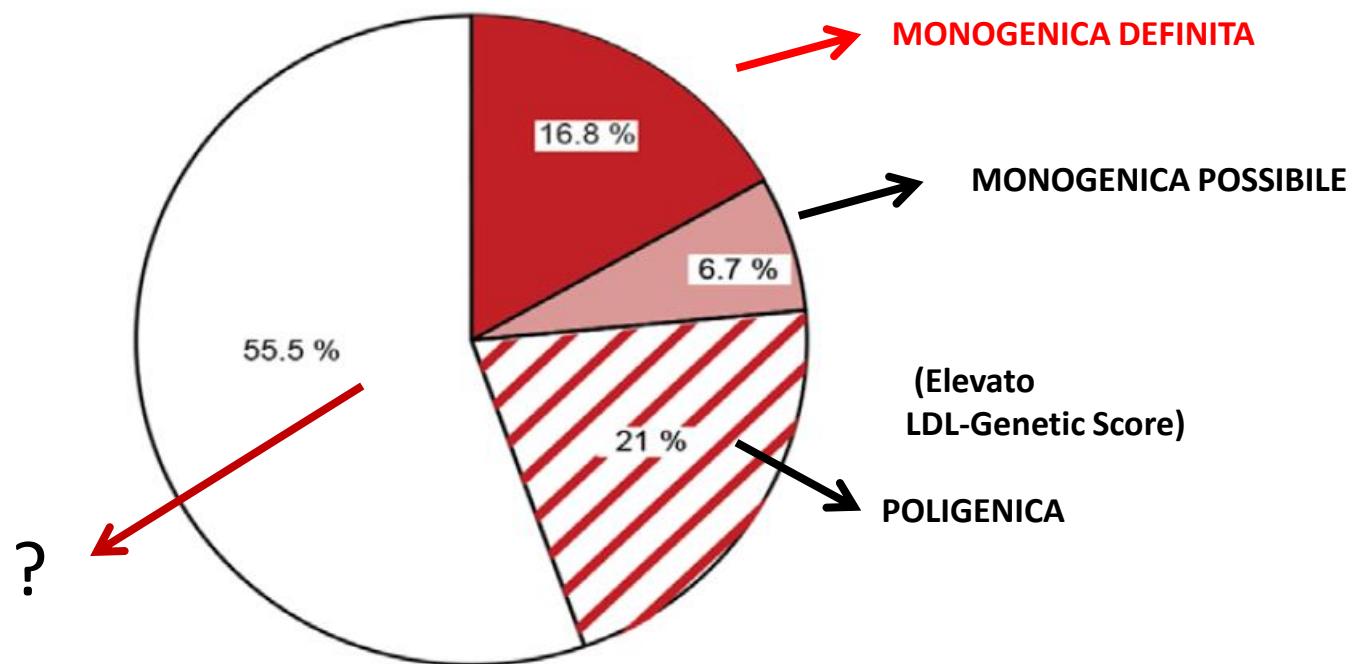
MAGGIORE SARÀ L'EFFETTO DI INCREMENTO DEI LIVELLI DI LDL.



LDL GENETIC SCORE

- █ Women with monogenic FH (n=20)
- █ Women with uncertain monogenic FH (n=8)
- █ Women with polygenic hypercholesterolemia (n=25)
- █ Women without genetic explanation (n=66)

119 Donne con LDL-C $\geq 99^\circ$



Profilo lipidico plasmatico.

Laura, 40 anni in ottima salute

- TC = 300 mg/dl
- TG = 60 mg/dl
- HDL-C = 50 mg/dl
- LDL-C = **238 mg/dl**

Manifestazioni cliniche associate

- Ipercolesterolemia primitiva
- Ipercolesterolemia Familiare (FH)
Monogenica o Poligenica

Storia familiare

} 45%

HUMAN GENETICS

Genetic identification of familial hypercholesterolemia within a single U.S. health care system

Science 354; 2016

Analisi genetica su 50,000 individui

PORTATORI DI VARIANTI PATOGENETICHE NEI GENI CANDIDATI PER FH MONOGENICA

Population characteristics	FH variant positive/total	Estimated prevalence
All DiscovEHR participants	229/50,726	1:222
Participants recruited from cardiac catheterization lab	57/6,747	1:118
Participants recruited from other sites	172/43,979	1:256

La variabilità fenotipica nella FH monogenica

FENOTIPO

LIVELLI DI LDL-C

XANTHOMI

CARDIOPATIA
ISCHEMICA

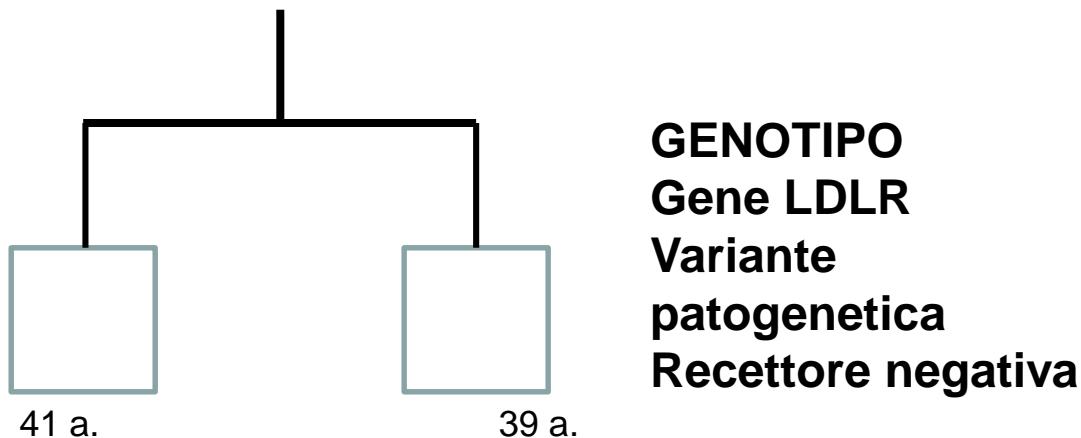
GENE CANDIDATO
COINVOLTO.
TIPO DI VARIANTE
PATOGENETICA

GENI MODIFICATORI
VARIANTI RARE
VARIANTI FREQUENTI

CONTRIBUTO
POLIGENICO (lipidi e non)

Fattori comuni di rischio
Cardio-Vascolare

Variabilità fenotipica in pazienti con FH monogenica



LDL-C = 293 mg/dl
CAD (-)

LDL-C 150 = mg/dl
CAD (-)

Varianti in alcuni geni modificatori il fenotipo FH

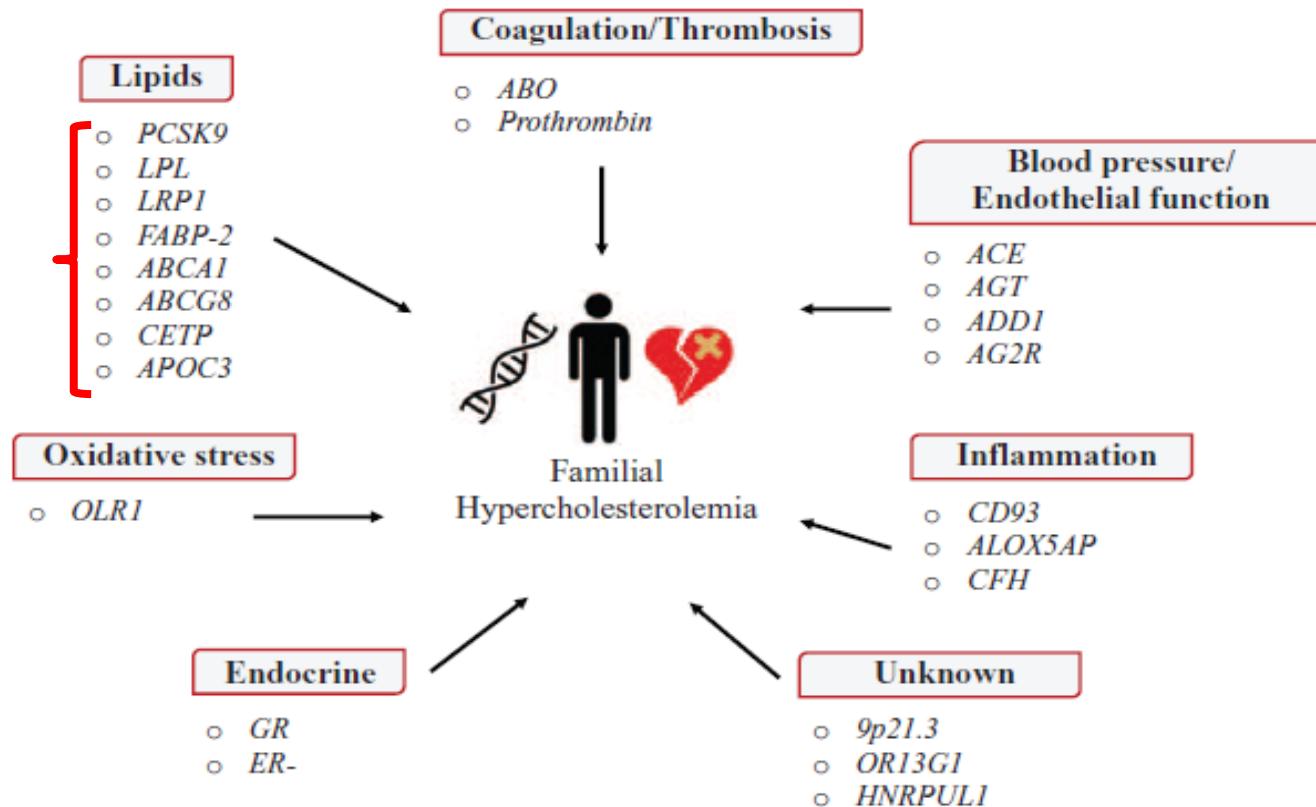
- Gene **APO B** (apoB anomale; es. troncate)
- Gene **NPC1L1** (assorbimento del colesterolo ↓)
- Gene **PCSK9** (ridotta interazione con LDLr)
- Gene **ANGPTL3** (ridotta secrezione/aumentato catabolismo delle LDL)



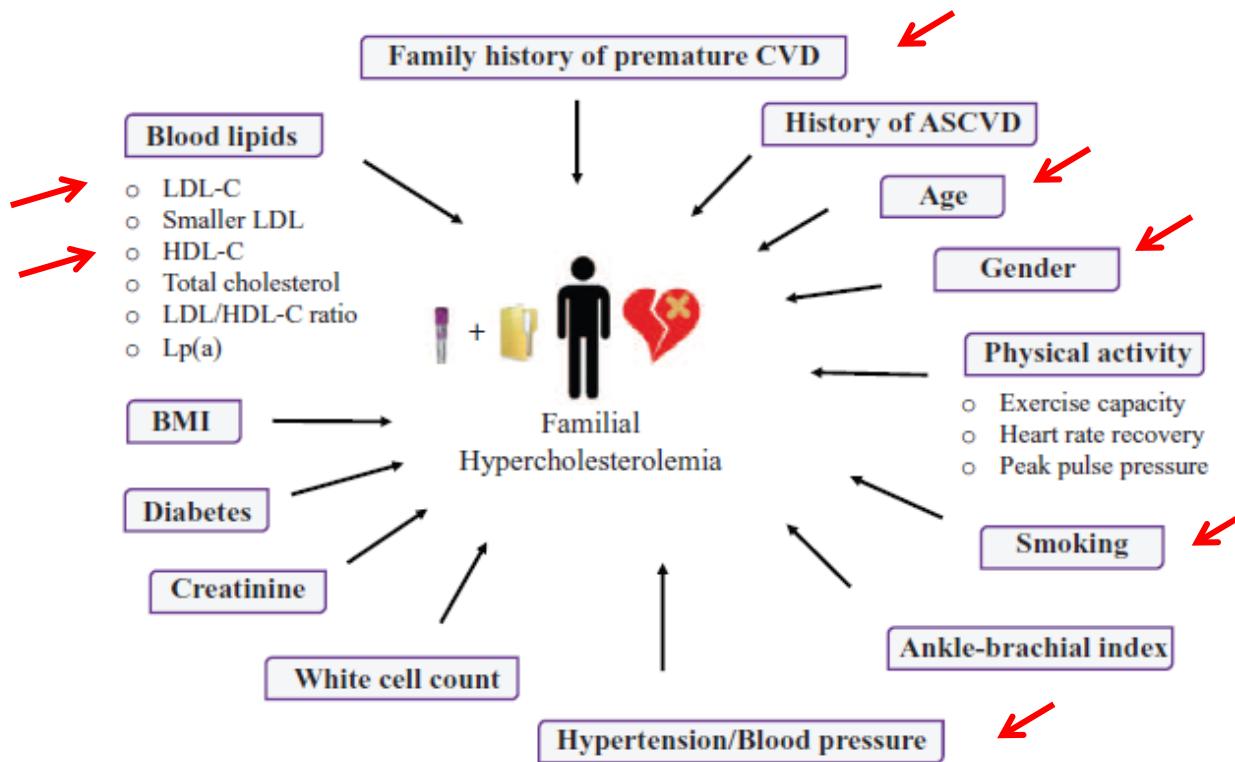
Familial
Hypercholesterolemia

A COMPLEX GENETIC DISORDER

EREDITA' POLIGENICA. GENI COINVOLTI NEL RISCHIO CARDIOVASCOLARE NELL'IPERCOLESTEROLEMIA FAMILIARE



FATTORI TRADIZIONALI DI RISCHIO CARDIOVASCOLARE NELLA IPERCOLESTEROLEMIA FAMILIARE



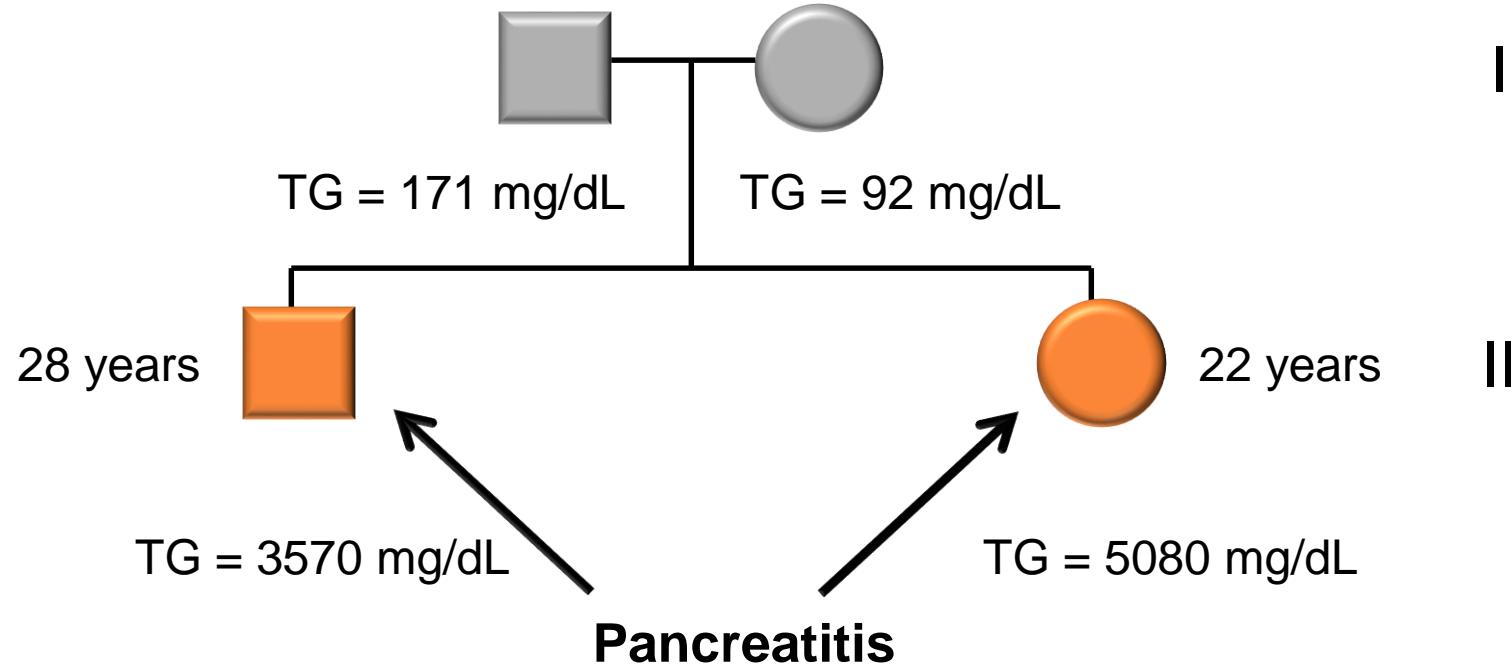
Agenda

- ◆ Definition
- ◆ Hyper and Hypolipidemias
- ◆ The severe hypercholesterolemic phenotype
 - ADH-1, 2, 3
 - LDLRAP1
 - Beta-sitosterolemia
 - Cholesterol 7 alpha hydroxylase deficiency
- ◆ The severe hypertriglyceridemic phenotype

HTG: clinical definition

Clinical definitions of hypertriglyceridaemia	Plasma triglyceride concentration (mmol/L)
2011 ESC/EAS guidelines	
Normal	<1.7
Hypertriglyceridaemia	1.7–9.9
Severe hypertriglyceridaemia	≥10
2001 NCEP ATP III guidelines	
Normal	<1.7
Hypertriglyceridaemia	
Borderline	1.7–2.3
High	2.3–5.6
Very high	>5.6
2012 Endocrine Society guidelines	
Normal	<1.7
Hypertriglyceridaemia	
Mild	1.7–2.3
Moderate	2.3–11.2
Severe hypertriglyceridaemia	
Severe	11.2–22.4
Very severe	>22.4

2 brothers with HyperTG pancreatitis



Marked Monogenic Elevations in Triglycerides are responsible for Familial Chylomicronemia

Gene	Disease	Inheritance	Frequency
LPL	Lipoprotein lipase deficiency	Autosomal recessive	1 in 1000000
APOCII	Apolipoprotein C-II deficiency	Autosomal recessive	rare
APOAV	Apolipoprotein A-V deficiency	Autosomal recessive	rare
GPIHBP1	GPIHBP1 deficiency	Autosomal recessive	rare
LMF1	Lipase maturation factor 1 deficiency	Autosomal recessive	rare

Monogenic Elevations in Triglycerides (Familial Hypertriglyceridemia)

Gene	Disease	Inheritance	Frequency
CREB3L3	Familial Hypertriglyceridemia	Autosomal Dominant	rare

Triglycerides in CREB3L3

Range: 74-4500 mg/dl

5 Kindred*

*Lee JH et Al, Nat Med. 2011

* Cefalù AB et Al Arterioscler Thromb Vasc Biol 2015

Agenda

- ◆ The severe mixed phenotype

Monogenic Elevations in Triglycerides and Cholesterol (Familial Dysbetalipoproteinemia)

Familial
Dysbetalipoproteinemia

Apo E2/E2

1-5/5000

Physical signs in Dysbetalipoproteinemia



Cholesterol

11.79 mmol/L (455 mg/dl)

Triglycerides

4.90 mmol/L (433 mg/dl)

Crit Rev Clin Lab Sci, 2014

Suggested algorithm for management of homozygous familial hypercholesterolaemia.

