FONDAZIONE S.I.S.A.

Per la promozione della ricerca sulle malattie da arteriosclerosi

Homozygous familial hypercholesterolemia New insights and guidance for clinicians

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

This meeting is endorsed by the European Atherosclerosis Society EAS

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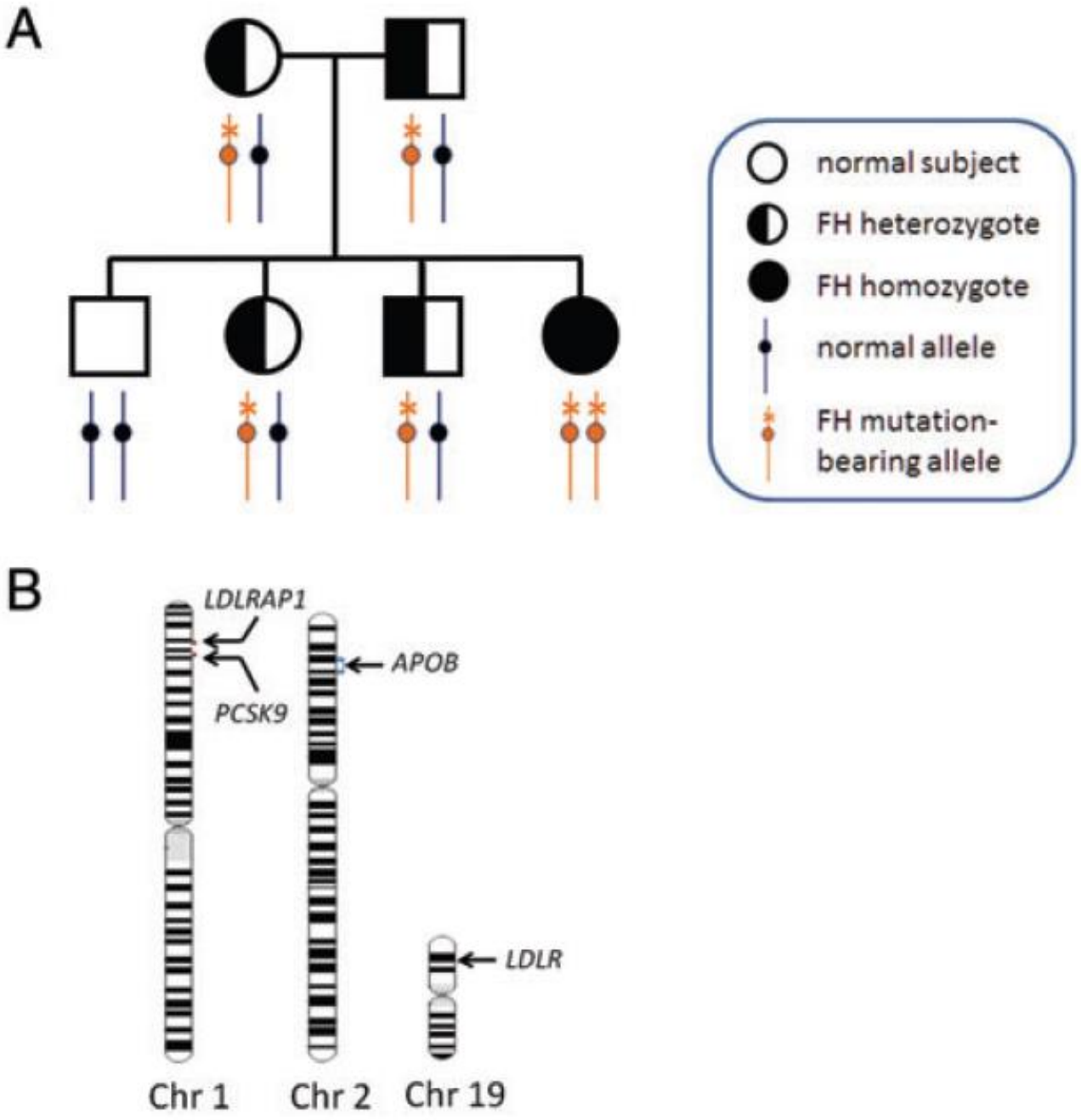
A
normal subject
FH heterozygote
FH homozygote
normal allele
FH mutation-bearing allele
B
LDLRAP1
PCSK9
APOB
LDLR
Chr 1
Chr 2
Chr 19

HOMOZIGOUS FAMILIAL HYPERCHOLESTEROLEMIA- HoFH

DOMINANT FORM

HOMOZIGOUS FAMILIAL HYPERCHOLESTEROLEMIA- HoFH

RECESSIVE FORMS

52 HO (25 M and 27 F) from Lebanon

- mean age 14.3 years; mean age of death 21 years in 21% of subjects
- cutaneous xanthomas 96% (elbows 90%, kness 85%, buttocks 79%, hands 75%); tendon xanthomas 100% (Achilles tendon 95%, dorsal hands 88%, periosteal 62%); arcus senilis 77%
- Aortic ejecton murmur 87%
- Born from a consanguineous marriage 58%
- Total cholesterol 750 ± 119 mg/dl (19.4 ± 3.1 mmol/L); range 510-999 mg/dl (13.2-25.8 mmol/L)

Khachadurian AK and Uthman SM Nutr Metabol 1973; 15: 132-40

Homozygous FH (HoFH)

- severe hypercholesterolemia with untreated LDL-C:
    - typically > 13 mmol/L 500 mg/dL up to 30 mmol/L
- xanthomata before age 10 years
- severe accelerated aortic and coronary atherosclerosis (1st - 2nd decades of life)
- LV outflow tract obstruction (AV or supra-AV)
- high mortality at an early age
- prevalence by genotype: ~ 1: 1,000,000

Homozygous autosomal dominant hypercholesterolaemia in the Netherlands: prevalence, genotype–phenotype relationship, and clinical outcome

- Prevalence of hoADH was estimated to be 1 : 300 000
- Mean LDL-C levels prior to lipid-lowering treatment were 12.9 mmol/L (range 4.4–21.5 mmol/L)
- Only 50% of the patients met the clinical criteria for hoADH (LDL-C >13.0 mmol/L)
- 29% of patients suffered from a CVD event

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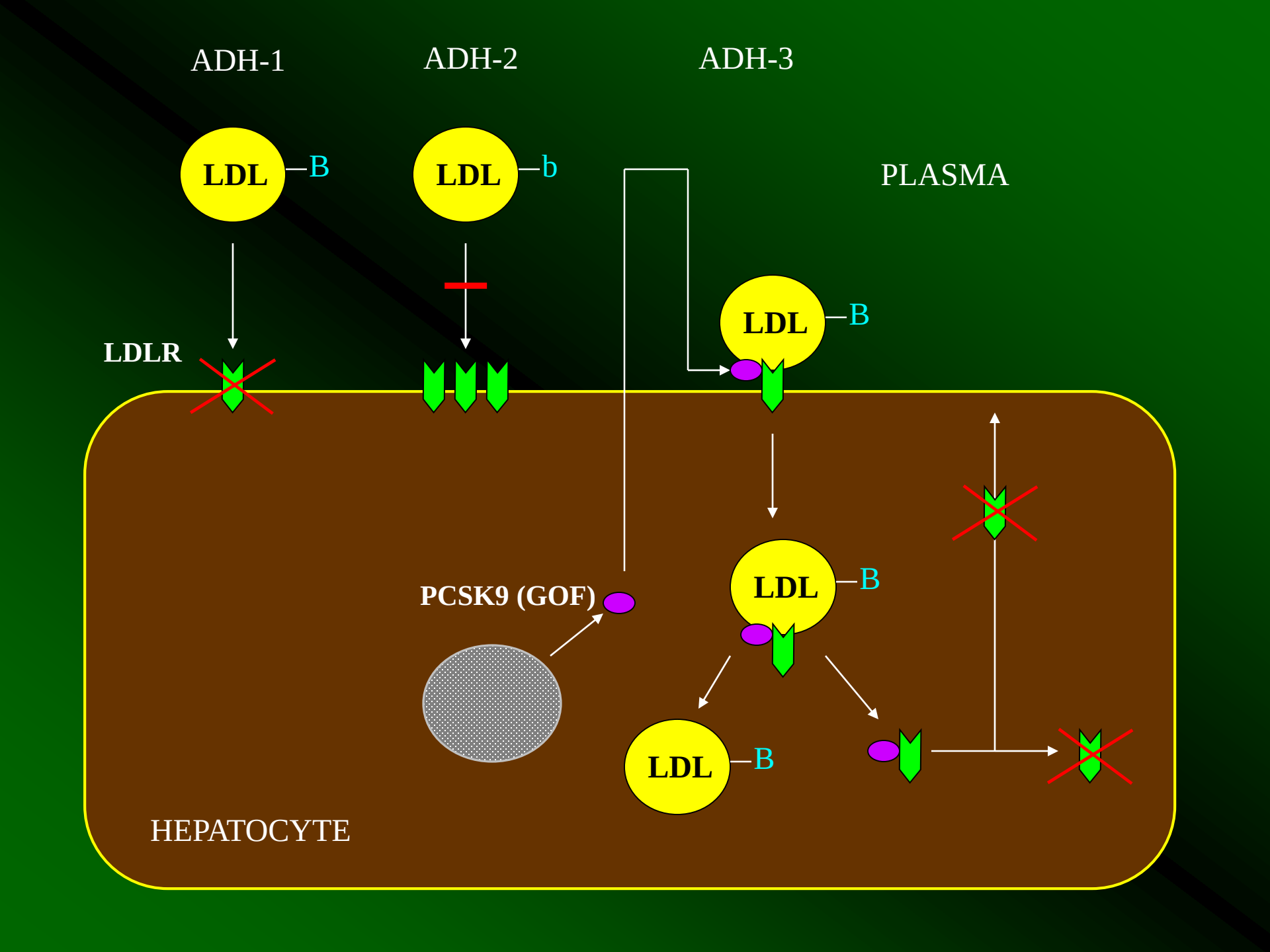
Familial ADH-HO/CHE

GENE	Disease
LDLR (19p13)	ADH-1 (FH)
APOB (2p24)	ADH-2 (FDB)
PCSK9 (1p32)	ADH-3


ADH-1
ADH-2
ADH-3
LDL
B
LDL
b
PLASMA
LDL
B
LDLR
PCSK9 (GOF)
LDL
B
LDL
B
HEPATOCYTE

CLINICAL DIAGNOSIS

- Tendon xanthomas, arcus cornea and cutaneous xanthomas (Planar and Tuberous) in the first decade of life (cutaneous xanthomas frequently present at birth, develop in almost all HO by age 4); interdigital xanthomas, particularly between the thumb and index finger
- generalized ATS during childhood (aortic root, coronary, carotid, iliac and femoral), severe stenosis of coronary ostia and major coronary arteries (righ, left anterior descending, left circumflex) before 20-25 years; valvular and supravalvular aortic stenosis
- acute joint attacks and joint deformities
- LDLc >13 mmol/L (>500 mg/dl); low HDLc; Tg slightly elevated in some subjects (defect of IDL removal)
- HCH in both parents
- family history of pCHD
- 2 mutant *LDLR* alleles

Criteria for the diagnosis of homozygous familial hypercholesterolaemia

- Genetic confirmation of two mutant alleles at the *LDLR*, *APOB*, *PCSK9*, or *LDLRAP1* gene locus

OR

- An untreated LDL-C >13 mmol/L (500 mg/dL) or treated LDL-C ≥8 mmol/L (300 mg/dL)* together with either:

○ Cutaneous or tendon xanthoma before age 10 years

or

○ Untreated elevated LDL-C levels consistent with heterozygous FH in both parents

* These LDL-C levels are only indicative, and lower levels, especially in children or in treated patients, do not exclude HoFH

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5 year-old HO-FH Italian boy with LDLc 1005 mg/dl

(Macchiaiolo M et al. Lancet 2012; 379: 1330)

Elbows	Knees	Tendons

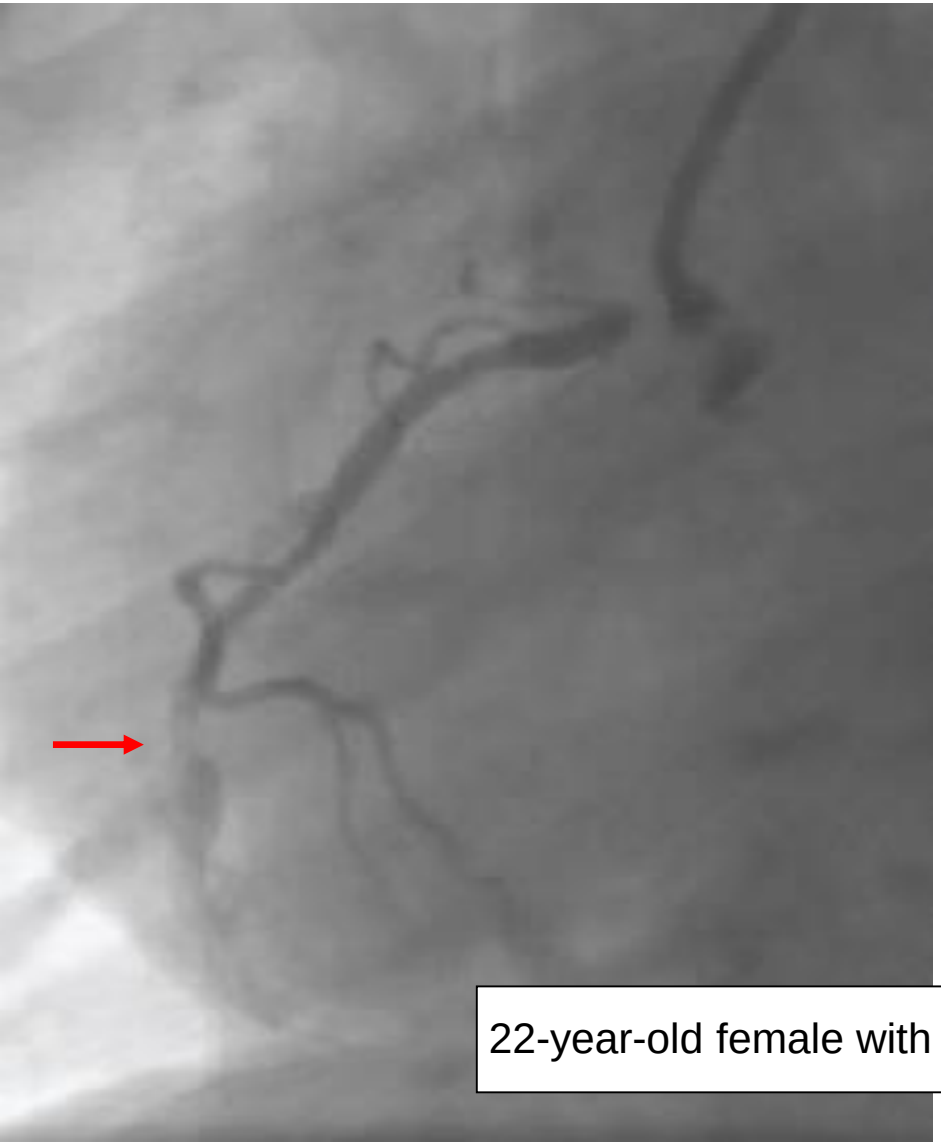
11 year-old HO-FH Asian-Indian boy with LDLc 595 mg/dl

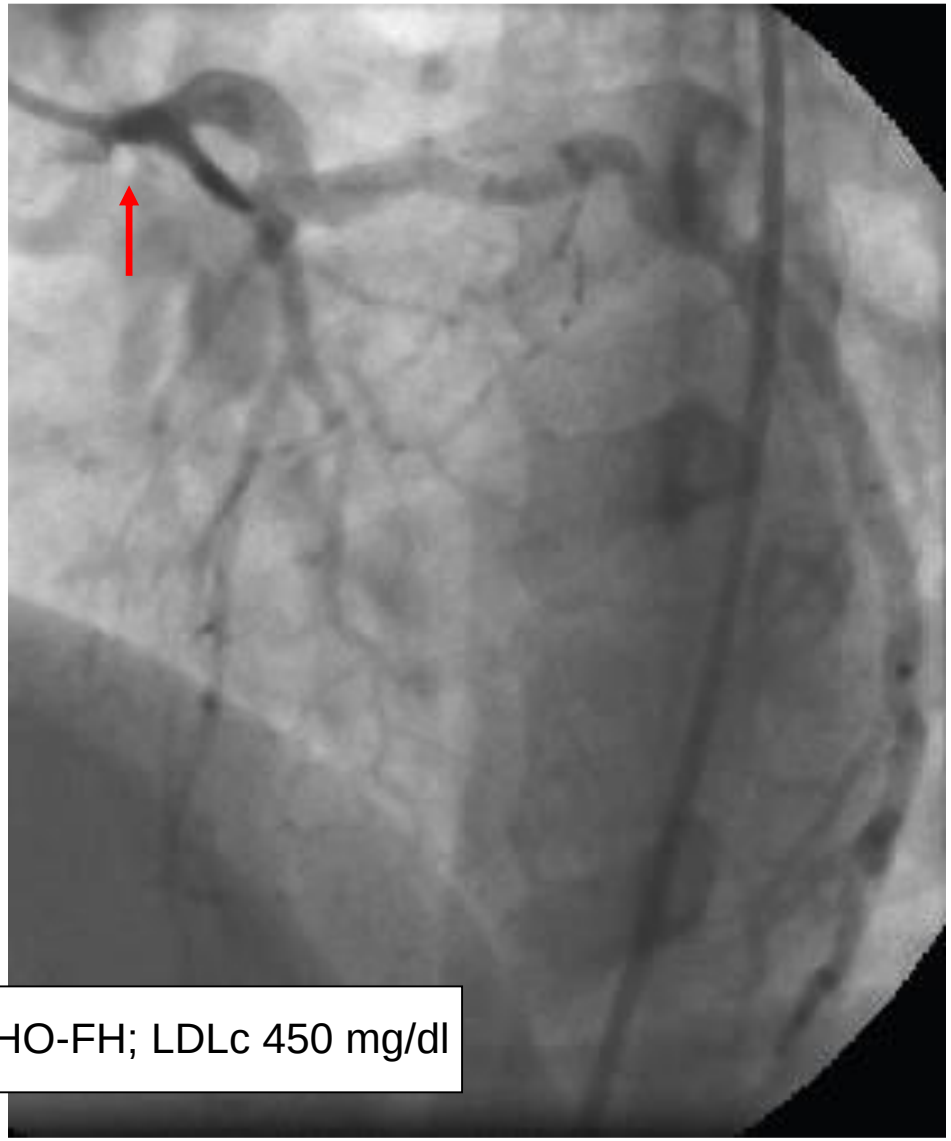
(Sethuraman G et al. Pediatr Dermatol 2007; 24: 230-234)

Interdigital planar xanthomas in a young patient with HO-FH

(Raal FJ et al. Atherosclerosis 2012; 223: 262-268)

Arcus cornea



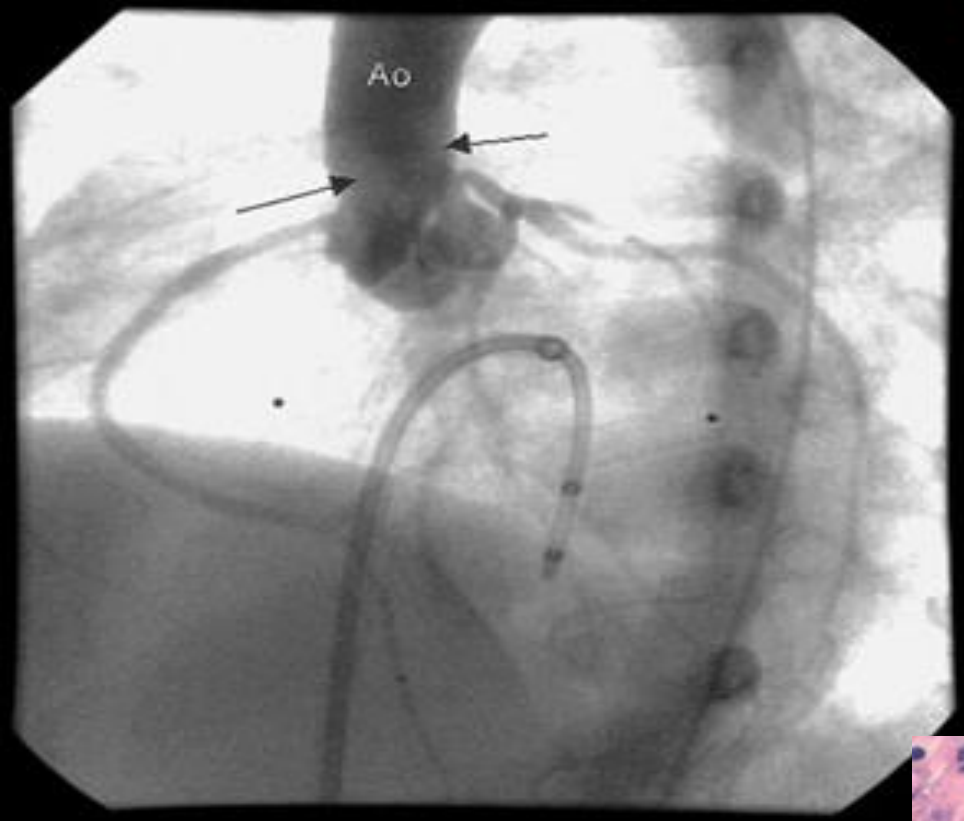


22-year-old female with HO-FH; LDLc 450 mg/dl

Critical ostial and mid portion stenosis of the right coronary artery

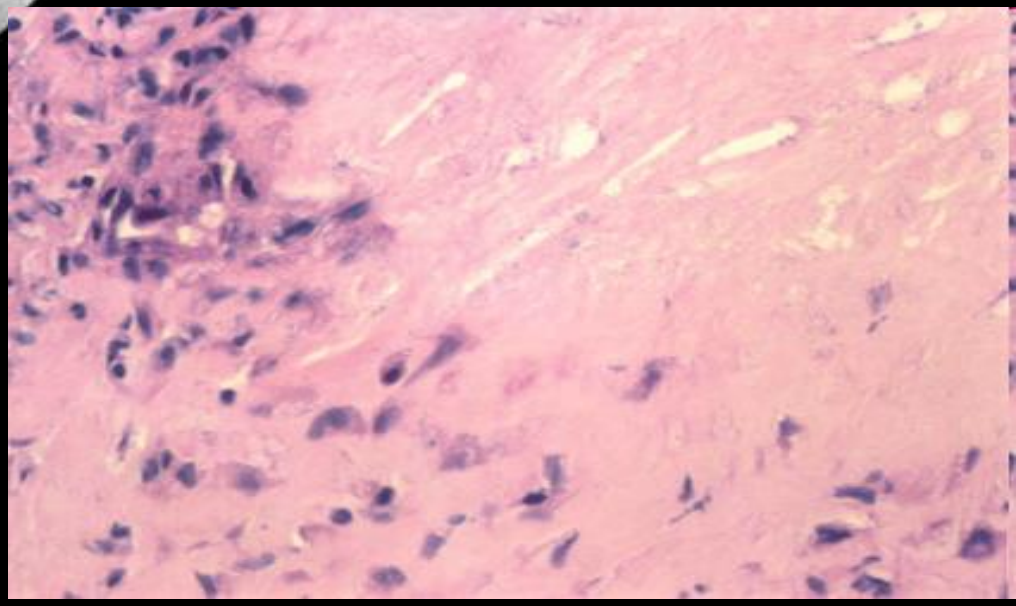
Moderate ostial stenosis of the LMCA on coronary angiography

(Can MM et al. ISRN Cardiology 2011)

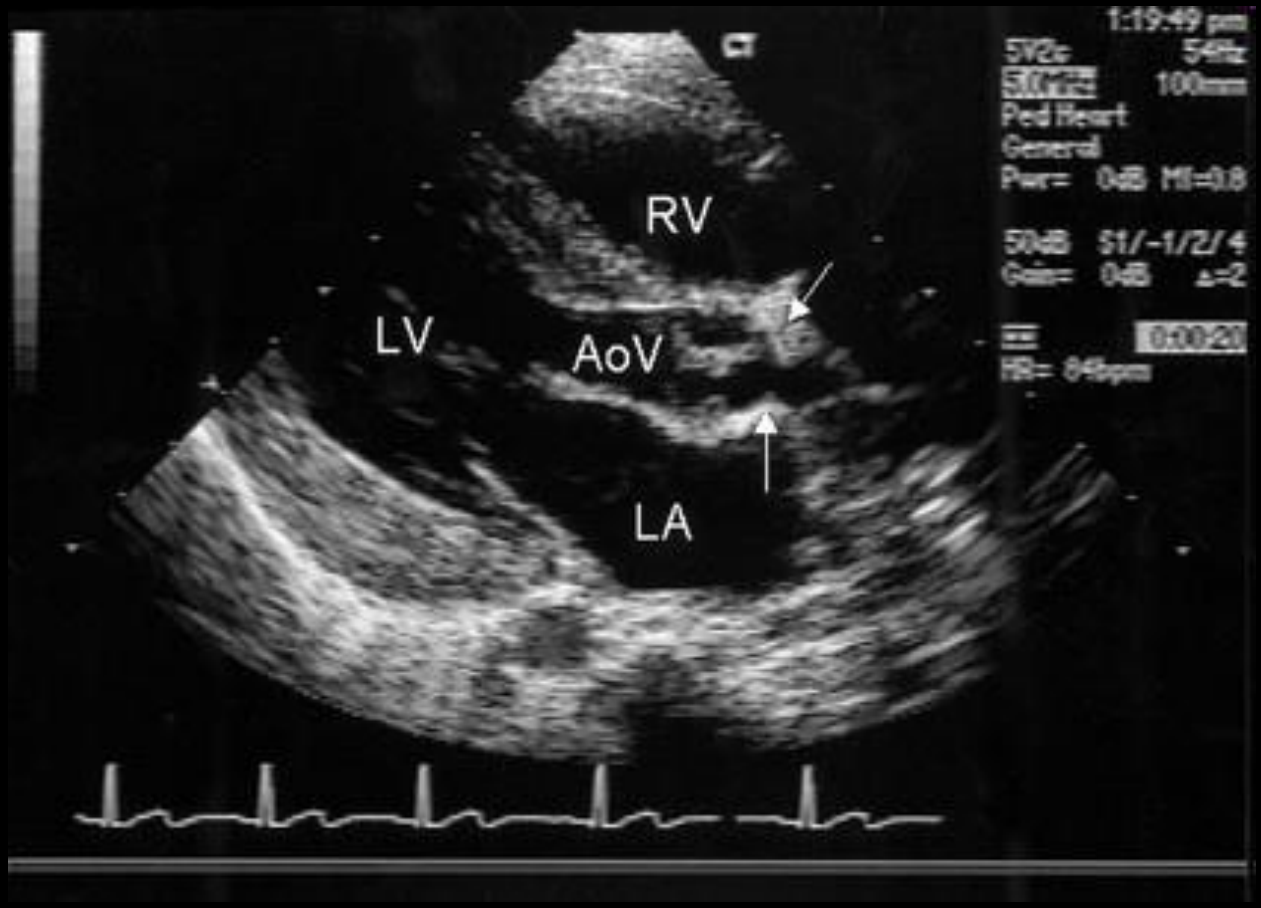


Angiogram showing supravalvular narrowing of ascending aorta

Atherosclerotic plaque with clear, elongated, needle-like cholesterol clefts and vacuoled lipid-laden macrophages

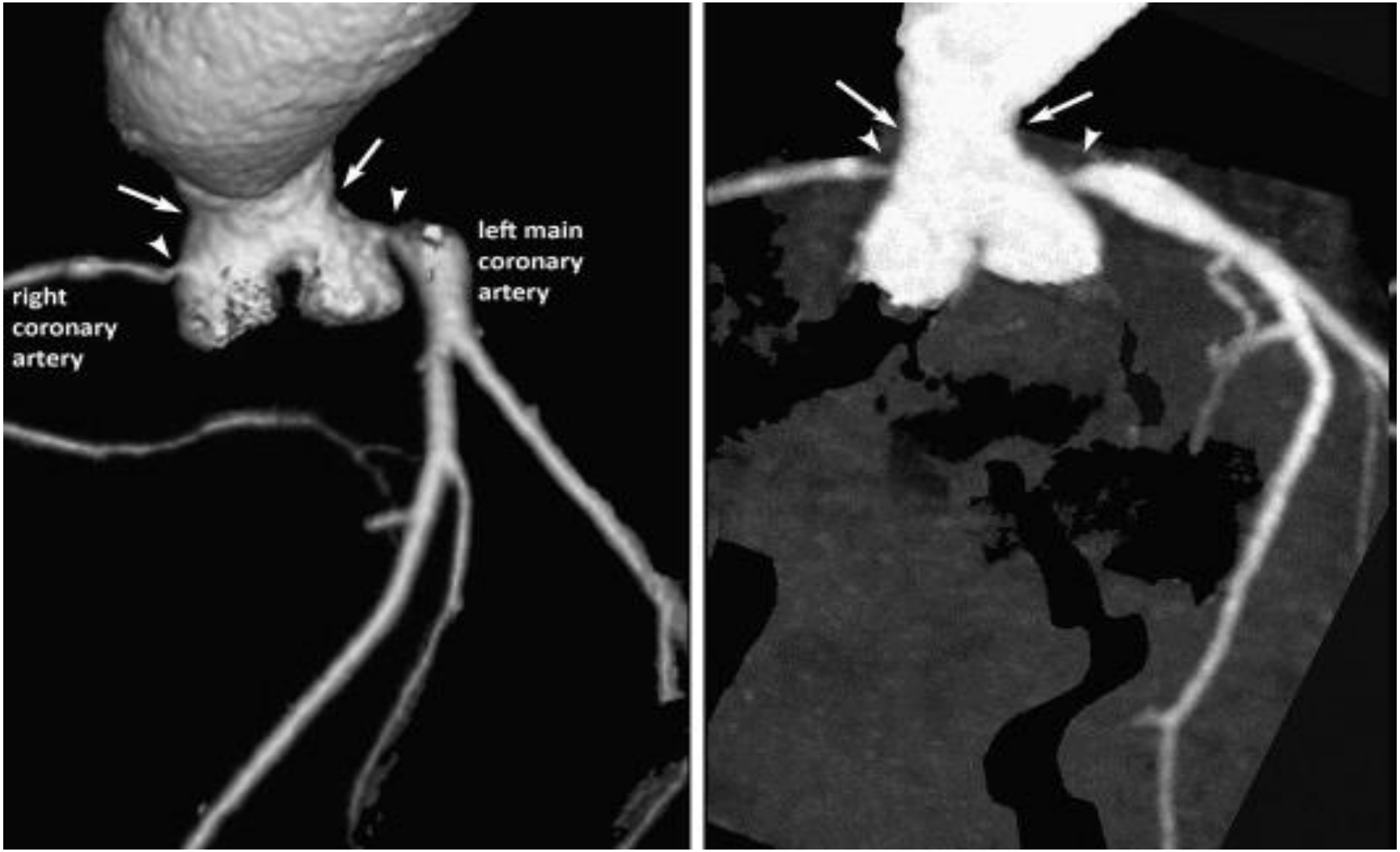


(Arora G et al. Pediatr Cardiol 2006; 27: 282-285)



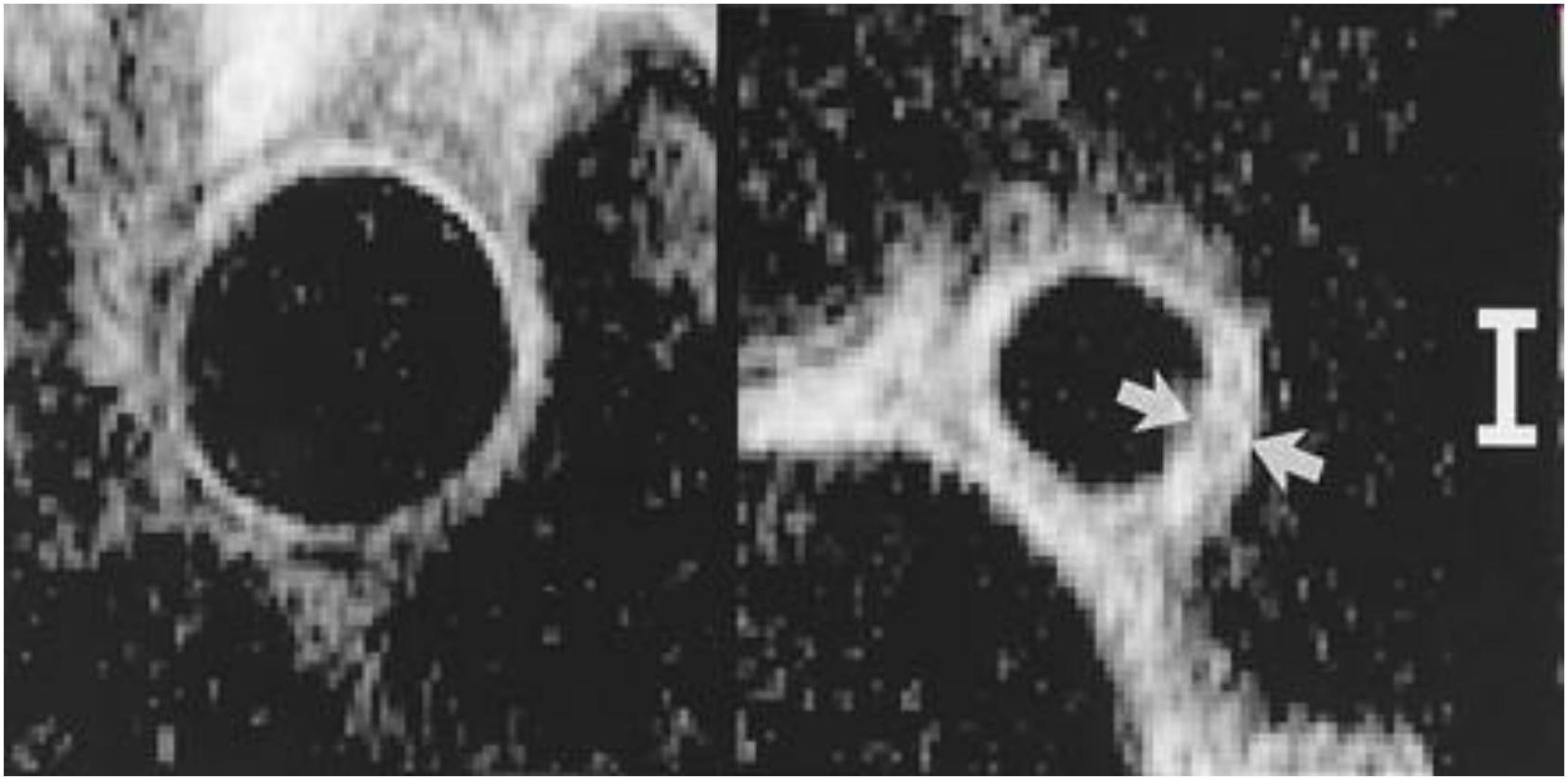
Echocardiogram showing supravalvular narrowing due to plaque deposition in a 5-year old boy with HO-FH (LDLc 788 mg/dl)

(Arora G et al. Pediatr Cardiol 2006; 27: 282-285)



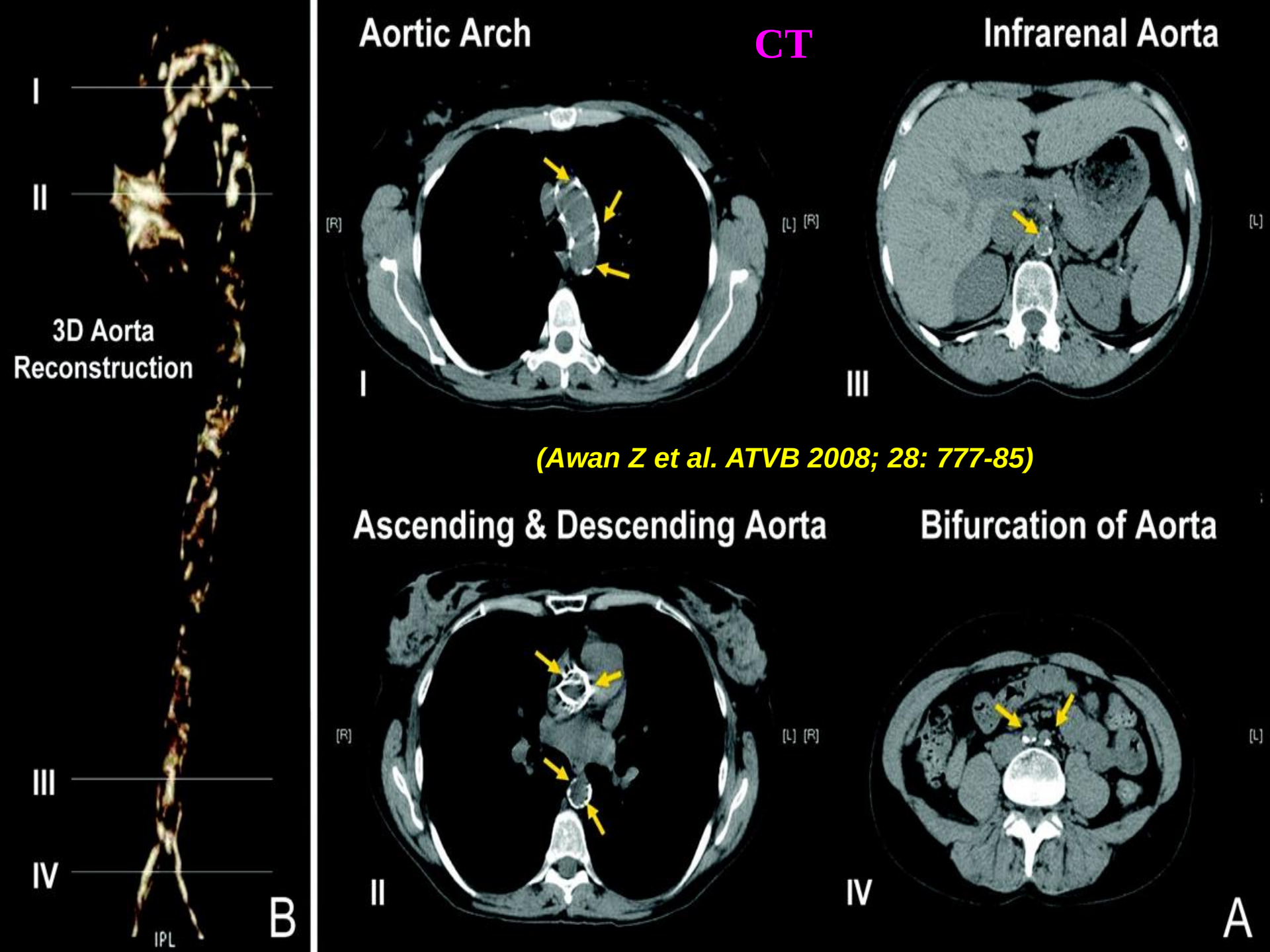
CT showing the aortic root with the supra valvular aortic stenosis, and the ostial left main coronary artery stenosis in a 14-year-old HO-FH girl died 10 years after liver transplantation

(El-Rassi I et al. J Clin Lipidol 2011; 5: 329-332)



Supravalvular aortic root evaluated by MRI in control subjects (n. 12) and in HO-FH (n. 17): average wall thicknees 2.3 ± 0.5 vs 3.3 ± 1.2 mm; supravalvular aorta transverse ID 25.4 ± 2.5 vs 19.9 ± 4.7 mm (focal plaques + medial hyperplasia); supravalvular aorta transverse OD 30.8 ± 2.8 vs 25.0 ± 4.8 mm (LDLR defect early in age arrested the growth of the ascending aorta).
In HO supravalvular stenosis 41%, plaques 86%.

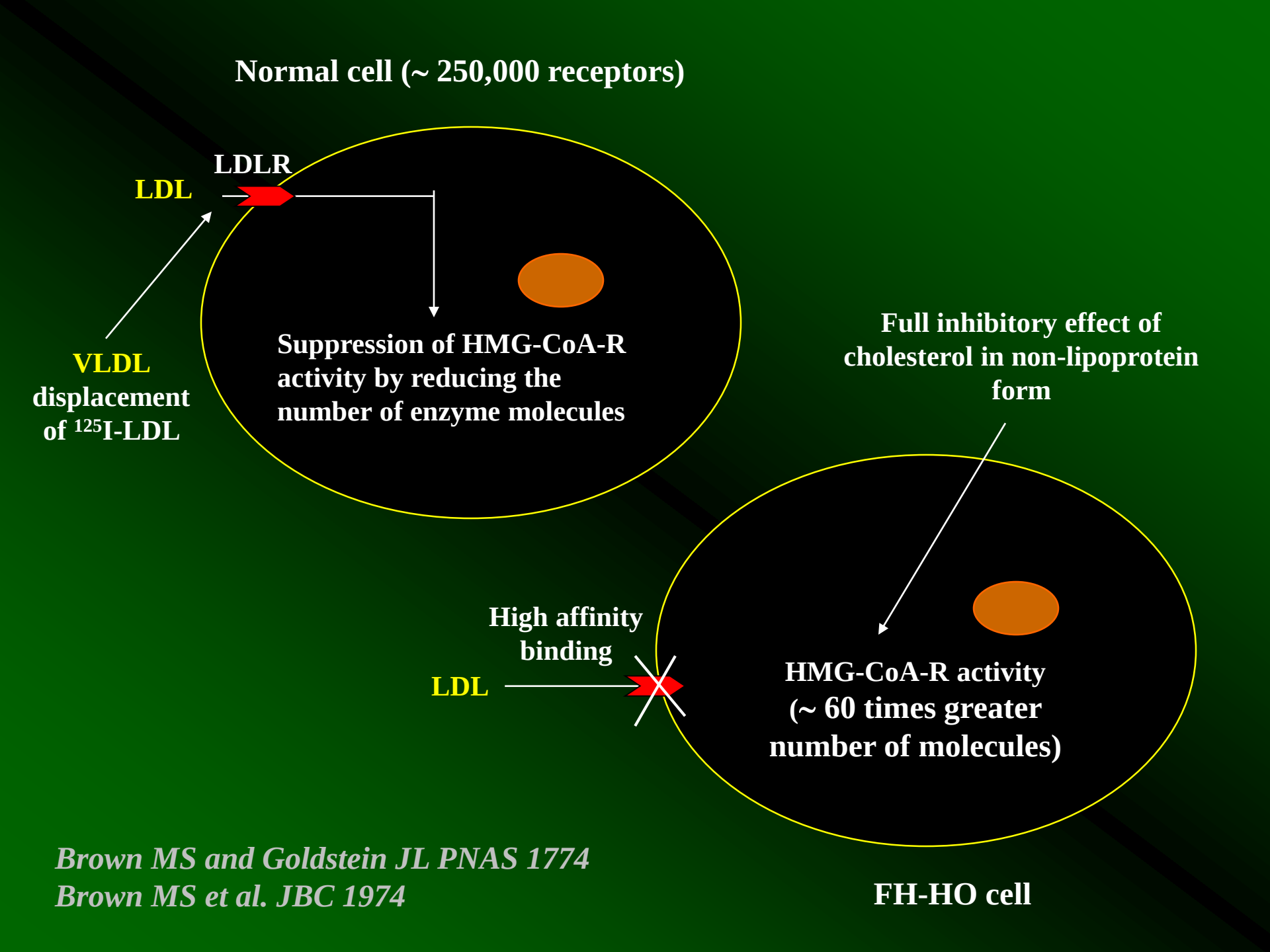
(Summers RM et al. Circulation 1998; 98: 509-518)



(Awan Z et al. ATVB 2008; 28: 777-85)

Total cholesterol levels in HO-ADH-1 patients

France	22.9 ± 4.8 mmol/L (n. 27)	885 mg/dl
England	21.8 ± 4.0 mmol/L (n. 22)	843 mg/dl
Germany	20.4 ± 3.3 mmol/L (n. 23)	789 mg/dl
Canada	20.4 ± 5.6 mmol/L (n. 44)	789 mg/dl
Turkey	19.9 ± 3.3 mmol/L (n. 30)	769 mg/dl
USA	19.4 ± 5.5 mmol/L (n. 47)	750 mg/dl
South Africa	18.2 ± 3.8 mmol/L (n. 130)	704 mg/dl
Tunisia	17.9 ± 3.4 mmol/L (n. 72)	692 mg/dl
Japan	17.6 ± 3.6 mmol/L (n. 70)	680 mg/dl
Lebanon	17.3 ± 3.5 mmol/L (n. 81)	669 mg/dl
China	17.0 ± 2.4 mmol/L (n. 23)	657 mg/dl
Italy	16.4 ± 4.5 mmol/L (n. 63)	634 mg/dl
Israel	15.7 ± 2.3 mmol/L (n. 18)	607 mg/dl



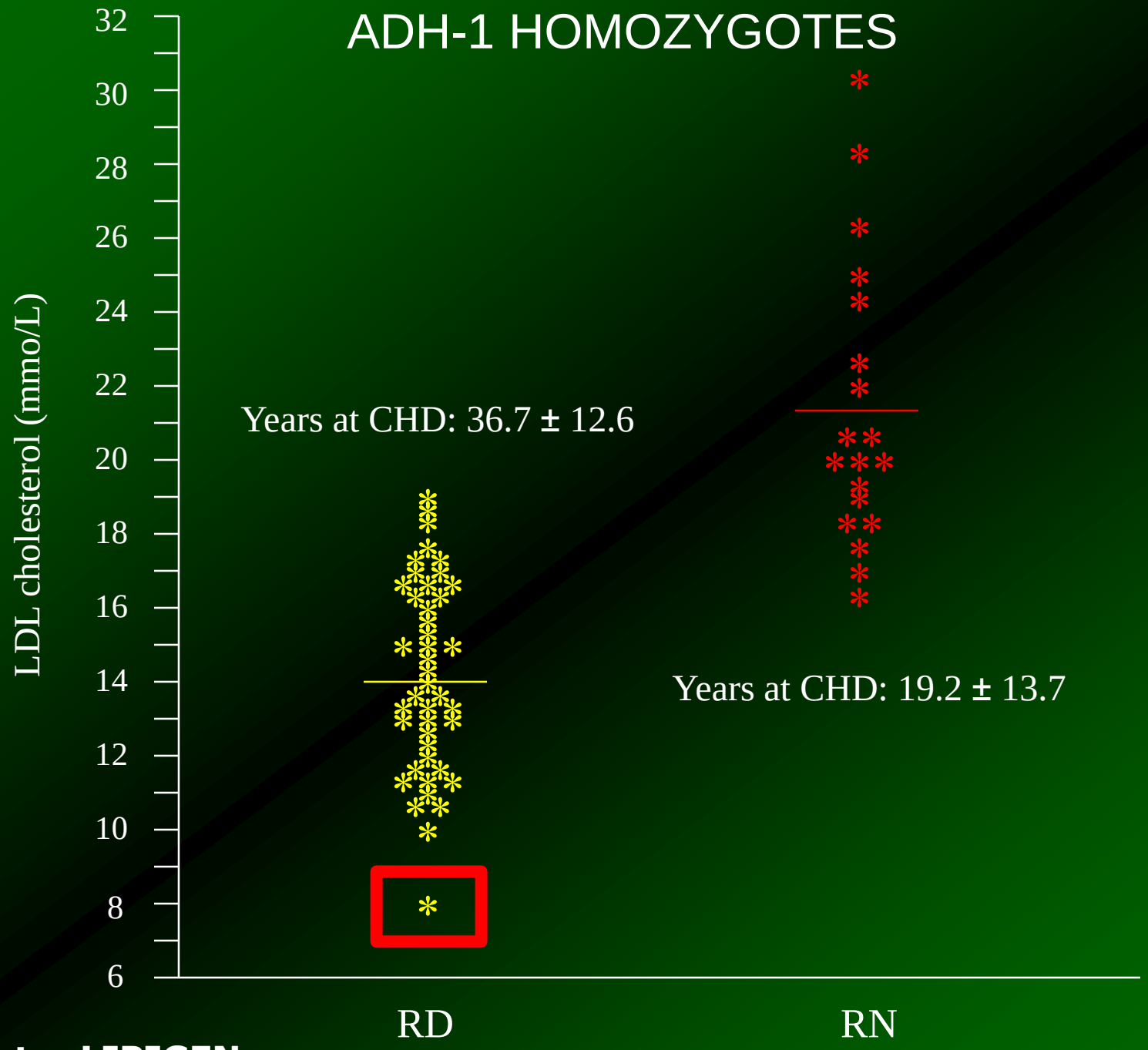
Brown MS and Goldstein JL PNAS 1774
Brown MS et al. JBC 1974

HO-RN (residual LDLR activity <5%): neither suppress HMGCoA-R activity nor stimulate cellular cholesterol esterification.

HO-RD (residual LDLR activity >5%): HMGCoA-R activity is partially suppressed and an increase in cholesterol esterification capacity is detectable in the presence of high lavels of LDL.

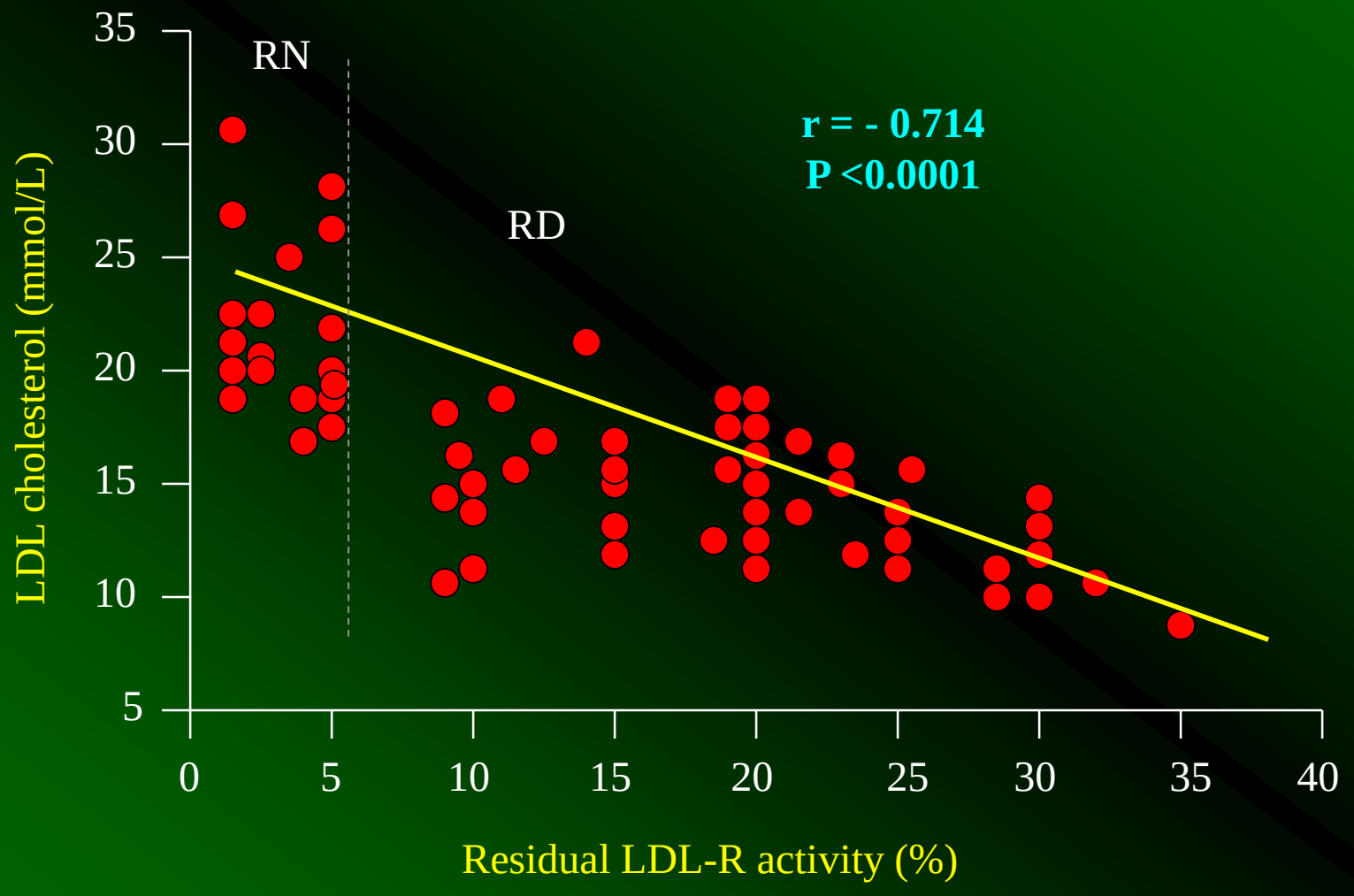
Goldstein JL et al. PNAS 1975; 72: 1092-6

ADH-1 HOMOZYGOTES



Il Registro LIPIGEN

Correlation between residual LDLR activity and plasma LDL-C in HO and CHE



ADH patients investigated (1993-2013)

- Clinical diagnosis of Homozygous ADH no. 63

CVD in HoFH

- HoFH <16 years:
  - ~10% clinical CVD
  - ~40% +ve coronary angiography (mild <50% single vessel)
  - ~40% aortic regurgitation
- ~90% of HoFH 16-30 years have clinical CVD
- athero imaging (angiogram, echo, CAC, carotid US) correlated with initiation age of lipid-lowering Rx
- LDL-apheresis over 7 years associated with:
  - 3.7-fold ↓CVD events
  - 20-fold ↓CV interventions

Kolansky *et al. Am J Cardiol* 2008; 102:1438-43
Sachais *et al. J Clin Apher* 2005; 20:252-5.

Cardiovascular complications of homozygous familial hypercholesterolaemia

- HoFH is characterized by accelerated atherosclerosis, typically affecting the aortic root, although other vascular territories may also be affected.
- The first major cardiovascular events often occur during adolescence, possibly younger when patients are *LDLR*-negative and/or untreated.
- In young children, early symptoms and signs are often linked to aortic stenosis and regurgitation, due to massive accumulation of cholesterol at the valvular levels.
- As aortic and supra-valvular aortic valve diseases may progress even when cholesterol levels are reduced, regular screening for subclinical aortic, carotid, and coronary heart disease is indicated.

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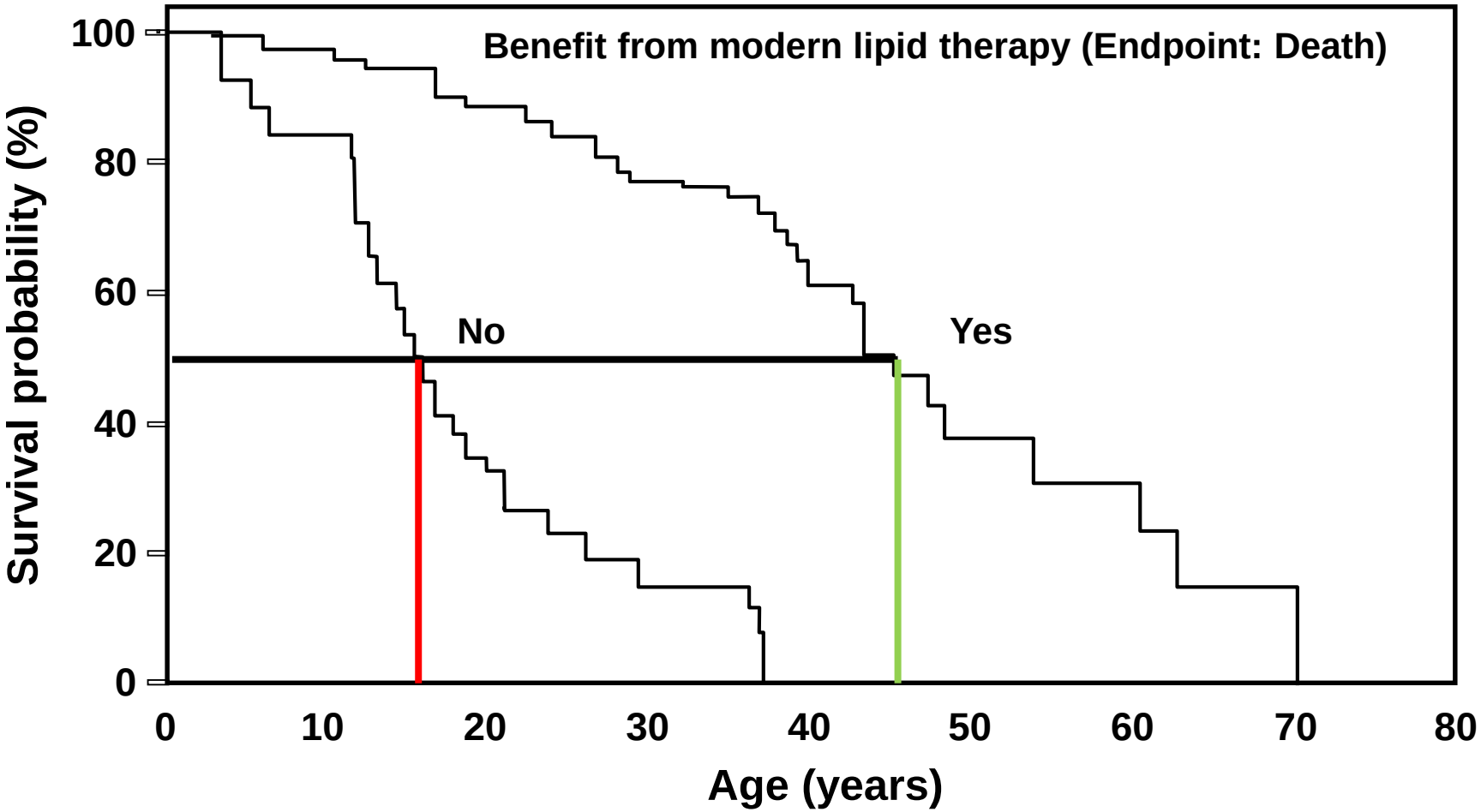
Cardiovascular mortality characteristics of patients with HoFH pre- statin(1990) and post-statin (n = 149)

	pre-1990 (n=36)	post-1990 (n=113)
Females/Males	24/12	58/55
Age at death – all causes (years)	18.4 ± 10.1 (n=27)	32.9 ± 15.5 (n=38) *
Age at death – CV (years)	17.7 ± 10.1 (n=22)	31.7 ± 13.3 (n=28) #

Results are expressed as mean ± SD
* $P<0.0001$ #$P<0.001$

Raal FJ *Circulation* 2011;124:2202-2207

Kaplan-Meier probability estimates of survival among HoFH patients before and after the introduction of modern lipid lowering therapy.



Raal FJ *Circulation* 2011;124:2202-2207

CVD in HoFH

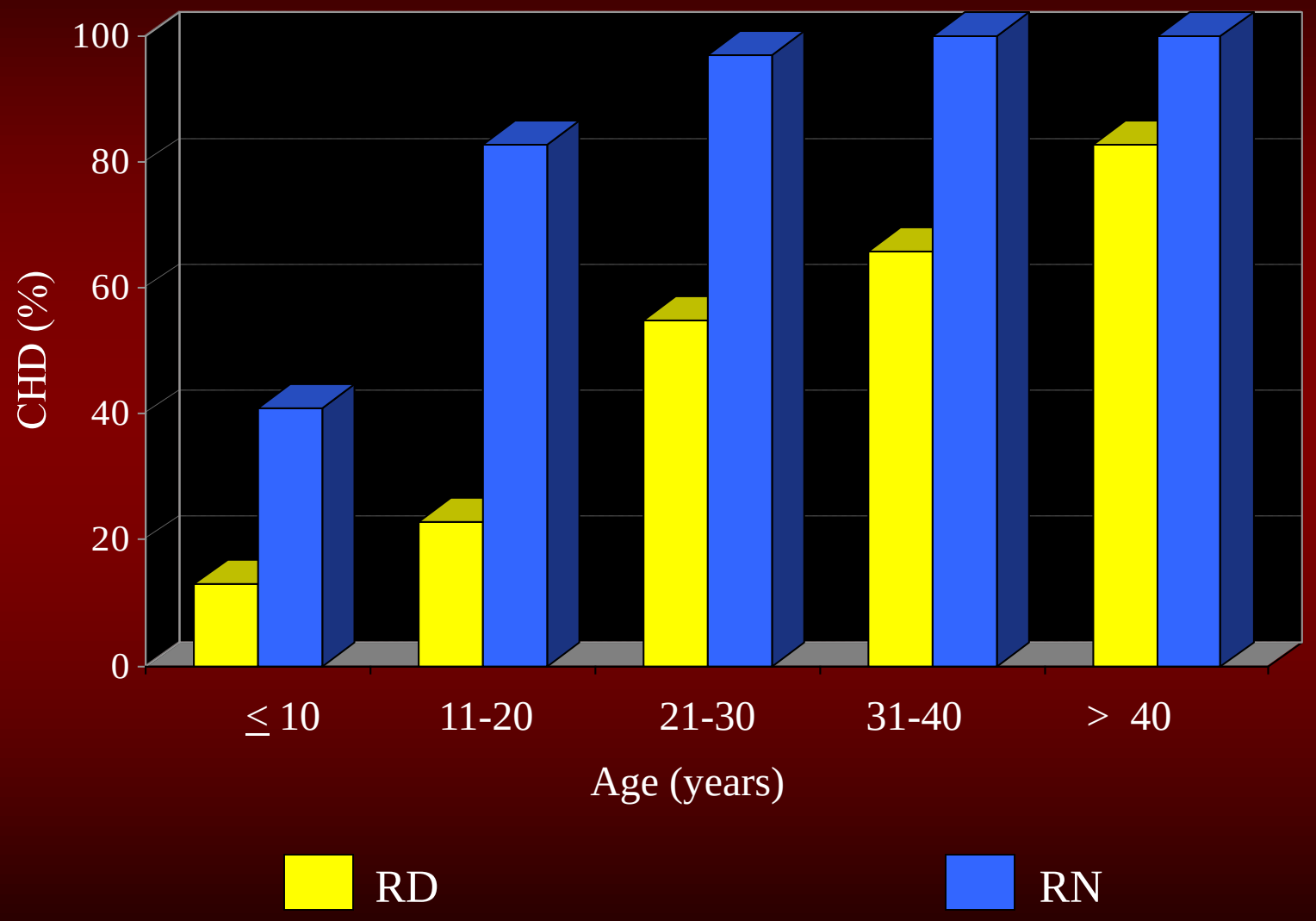
Recent follow-up data on use of LDL apheresis in homozygous familial hypercholesterolaemia.

	Ref [7]	Ref [5]	Ref [6]
Homozygotes, *n*	39 (22[a])	27[b]	29[c]
On apheresis, *n*	17	27	20
Age started (years)	7	8.5	9
Duration (years)	6.6	12.6	6
Baseline cholesterol (mmol/l)	20.5 (TC)	23 (TC)	21 (LDLC)
Δ baseline chol with aph/drugs	−45%	−51%	−55%
CVD present pre-Rx	9%[a]	48%	60%
CVD developed during Rx	35%[a]	22%	20%

n, number; TC, total cholesterol; LDLC, LDL cholesterol.

Thompson *et al.* *Atherosclerosis* 2010; 208:317-21

Percent prevalence of CHD in patients with HO-ADH-1 (231 RD and 242 RN)



HDL in HO-ADH-1

- Elevated concentrations of small preβ-HDL particles and reduced levels of large HDL-2 particles;
- HDL are enriched in CE and depleted in PL with an increase in the Sphingomyelin/Phosphatidylcholine (SM/PC) ratio;
- Reduced plasma efflux capacity from macrophages to HDL-2 and HDL-3 SR-BI-mediated and to HDL-2 ABCG1-mediated (the reduced efflux is related to the reduced PC content).

Guerin M. Curr Opin Lipidol 2012; 23: 377-85

	LDL chol. (mmol/L)	HDL chol. (mmol/L)
ADH-1 homozygotes	17.55 ± 4.85	0.76 ± 0.32
ADH-2 homozygotes	8.23 ± 1.31	1.00 ± 0.15
ADH-1/ADH-2 compound heterozygotes	10.69 ± 3.14	1.16 ± 0.40
ADH-1/ADH-3 compound heterozygotes	11.06 ± 2.74	1. 27 ± 0.36
ADH-1 heterozygotes	7.25 ± 1.70	1.30 ± 0.34
ADH-2 heterozygotes	6.21 ± 1.50	1.31 ± 0.37
ADH-3 heterozygotes	8.08 ± 2.75	1.27 ± 0.44

mean±SD

Lp(a) levels in HO and HE-ADH-1

	HO-ADH-1	HE-ADH-1	Controls
N.	26	43	100
Mean	49.9	29.9	23.2
Median	36.6	14.4	11.2
K-IV repeats	Mean		
15-20	64.8	73.6	35.0
21-25	22.7	10.9	12.5
26-30	17.2	10.4	8.0
31-35	18.1	9.8	9.0
36-45	10.6	2.6	1.5

Reduced catabolism and/or increased biosynthesis

Kraft HG et al. ATVB 2000; 20: 522-8

Clinical features in 63 ADH-1 homozygotes

	ALL	LDL-RD	LDL-RN	P
M/F	30/33	29/15	11/8	NS
HO/CHE	40/23	29/15	6/13	NS
Age (years)	24.1 ± 16.4	27.7 ± 16.2	15.8 ± 13.9	0.007
Tc (mmol/L)	17.90 ± 4.51	15.82 ± 2.78	22.75 ± 4.05	0.0001
LDLc (mmol/L)	16.43 ± 4.56	14.30 ± 2.80	21.39 ± 4.02	0.0001
HDLc (mmol/L)	0.86 ± 0.24	0.93 ± 0.23	0.72 ± 0.21	0.001
Tg (mmol/L)	1.25 ± 0.45	1.19 ± 0.44	1.37 ± 0.44	NS
Px	50.8%	40.9%	73.7%	0.03
Tux	60.3%	52.2%	78.9%	0.05
Tx	93.6%	95.4%	89.5%	NS
CHD	60.3%	52.2%	78.9%	0.05

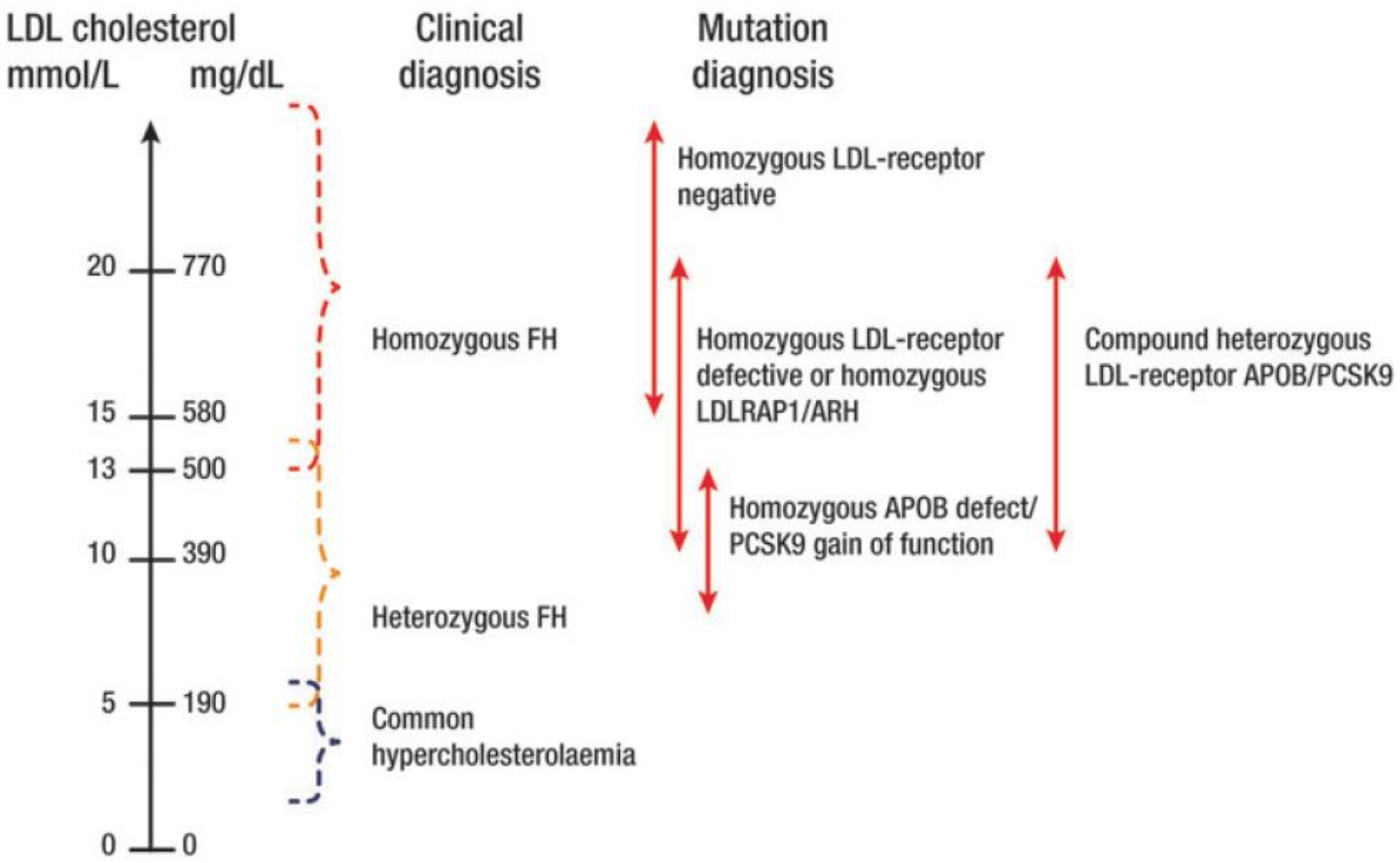
Parameters significantly associated with CHD in 63 HO/CHE ADH-1 patients (Italian Lipid Clinics) by Multiple Logistic Regression Analysis

Parameter	β±SE(β)	OR	95% CI (OR)	P
Age (10 years)	1.31±0.36	3.73	1.82-7.65	0.0001
LDLc (quartiles)	0.73±0.35	2.07	1.03-4.15	0.04
HDLc (quartiles)	-1.06±0.40	0.34	0.15-0.77	0.009

Parameter	β±SE(β)	OR	95% CI (OR)	P
Age (10 years)	1.31±0.37	3.71	1.80-7.66	0.0001
RN vs RD	2.18±0.88	8.86	1.56-50.42	0.02
HDLc (quartiles)	-0.98±0.41	0.37	0.16-0.84	0.02

FOLLOW UP OF HOMOZYGOUS ADH-1

		Age at molecular diagnosis (years)	Present age or age at death (years)
RD (n. 44)	Still alive (n. 29) (66%)	24.3 ± 16.6	32.9 ± 14.8
	Deceased (n. 4)	39.7 ± 11.2	44.5 ± 13.1
	Lost at follow-up (n. 11)	33.4 ± 12.3	
RN (n. 19)	Still alive (n. 11) (58%)	10.6 ± 9.2	21.9 ± 11.2
	Deceased (n. 5)	24.2 ± 20.5	28.0 ± 25.5
	Lost at follow-up (n. 3)	20.6 ± 11.0	


LDL cholesterol
mmol/L
mg/dL
Clinical diagnosis
Mutation diagnosis
20
770
15
580
13
500
10
390
5
190
0
0
Homozygous FH
Heterozygous FH
Common hypercholesterolaemia
Homozygous LDL-receptor negative
Homozygous LDL-receptor defective or homozygous LDLRAP1/ARH
Homozygous APOB defect/ PCSK9 gain of function
Compound heterozygous LDL-receptor APOB/PCSK9

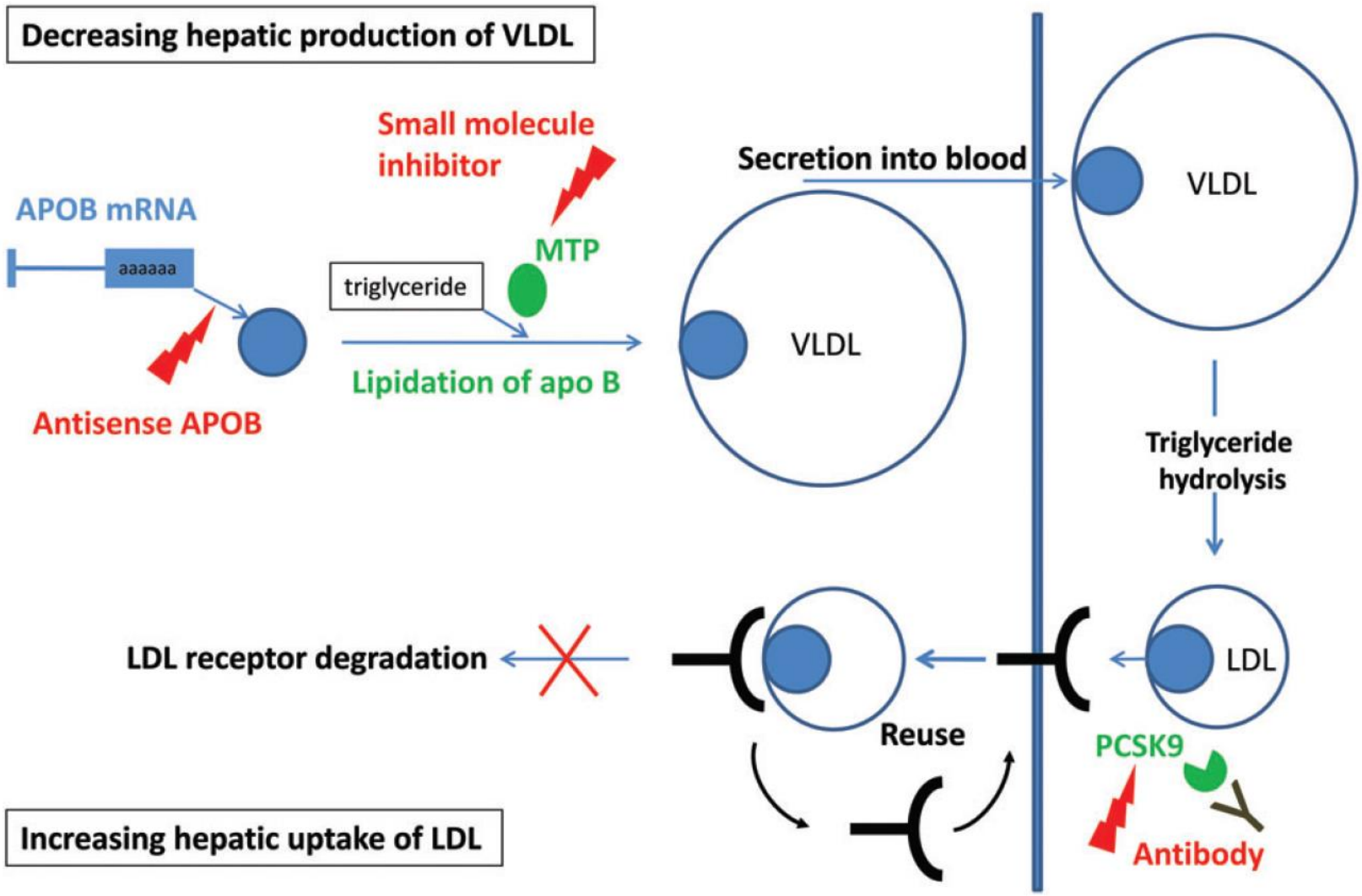
ADH-HO/CHE

ADH-1 (HO/CHE)	96.4%
ADH-2 (HO)	0.7%
ADH-3 (HO)	0.2%
ADH-1/ADH-2 (CHE)	1.7%
ADH-1/ADH-3 (CHE)	1.0%

Prenatal diagnosis for HO-ADH-1

Authors	Sampling	Method	Outcome
Brown et al. (Lancet 1978)	Amniocentesis at the 15th week	Assay of LDLR activity in cultured amniotic-fluid cells (19th week)	HO-ADH-1 therapeutic abortion at the 20th week
De Gennes et al. (Arteriosclerosis 1985)	Fetal blood sampling from umbilical cord at the 18-24th week	Fetal blood cholesterol assay at the 18-24th week	HO-ADH-1 therapeutic abortion at the 18-24th week
Bertolini et al. (Hum Genet 1993)	Transabdominal chorionic villus sampling at 10th week	Analysis of LDLR gene at 11th week	Healthy fetus

Novel lipid-regulating drug targets



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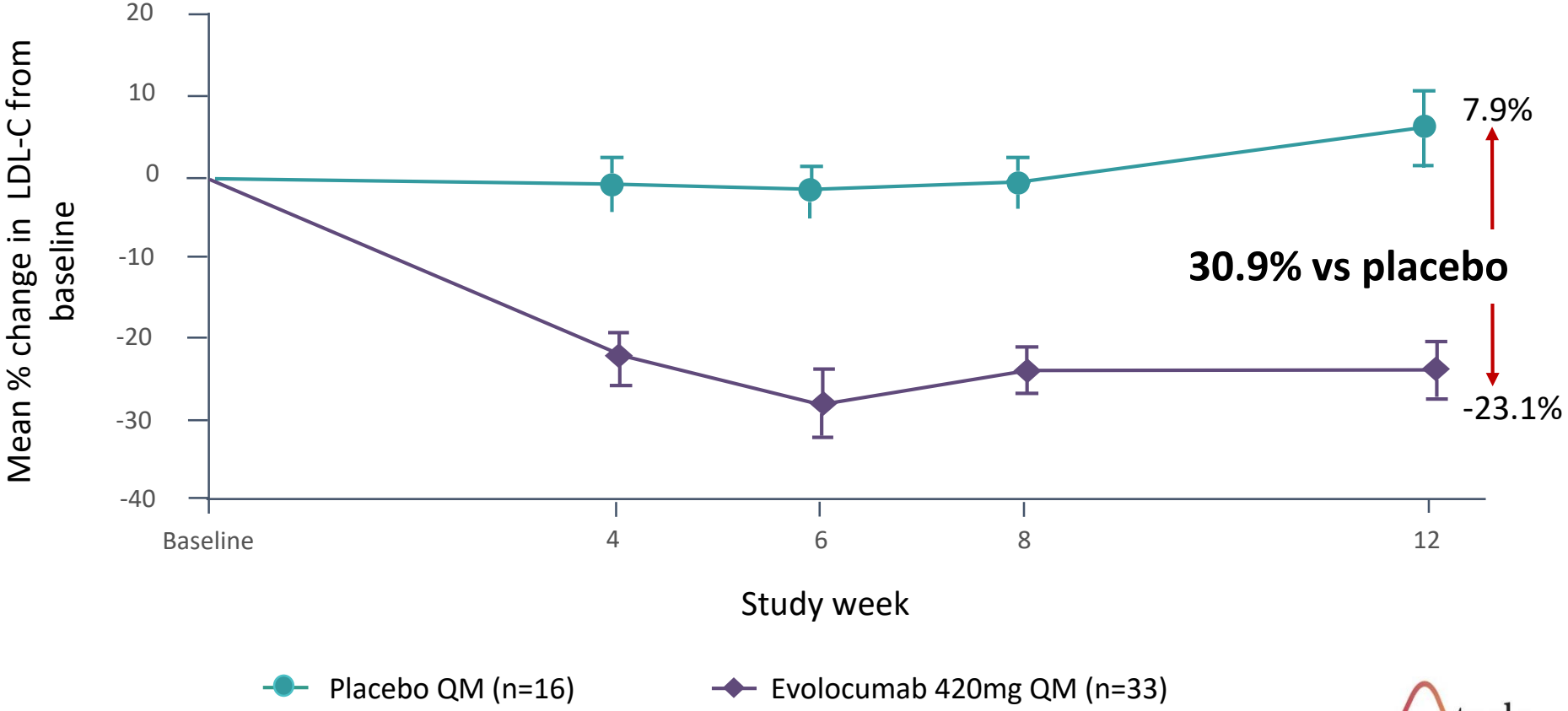
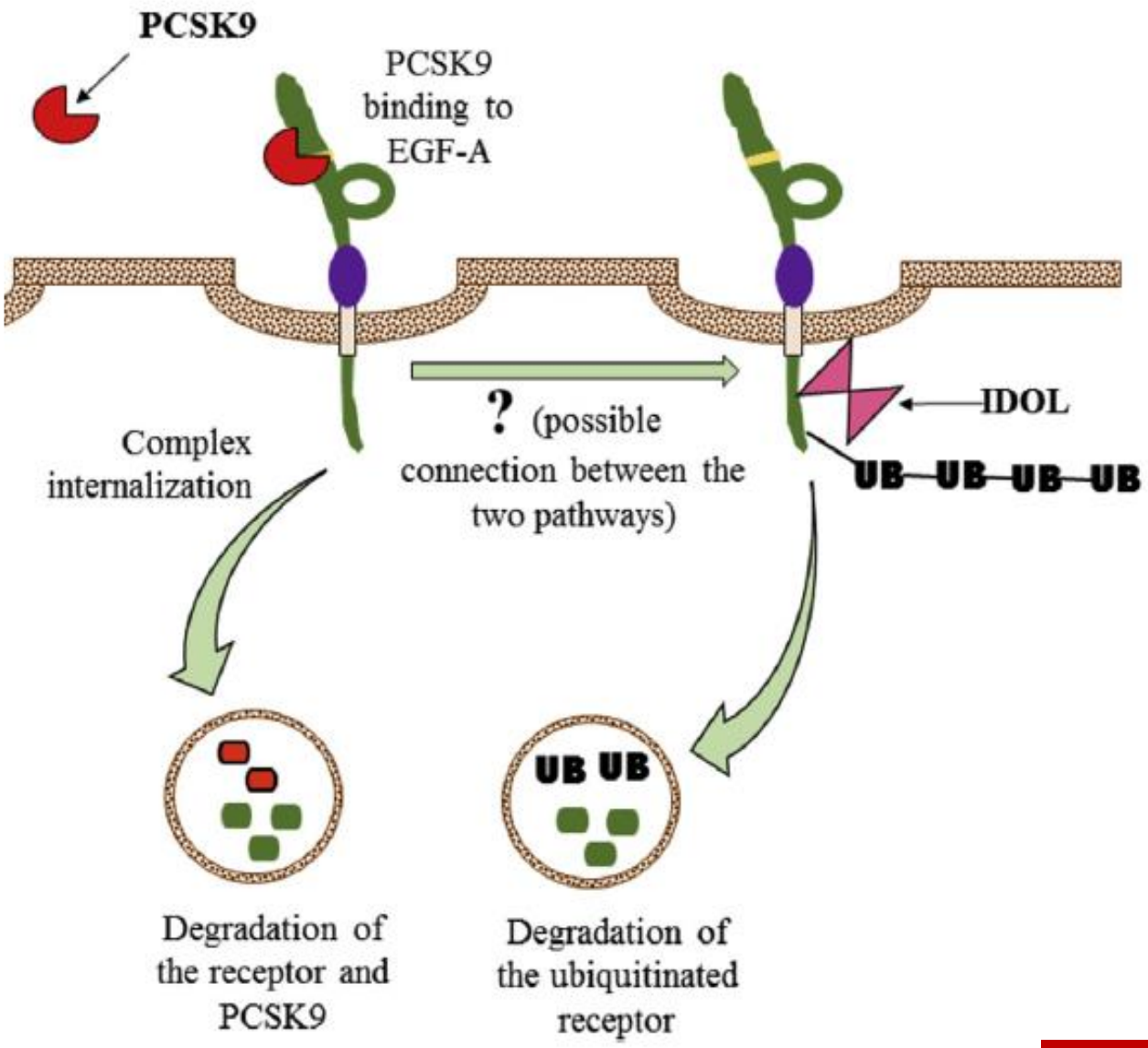
Evolocumab significantly reduces LDL-C even in patients with homozygous FH



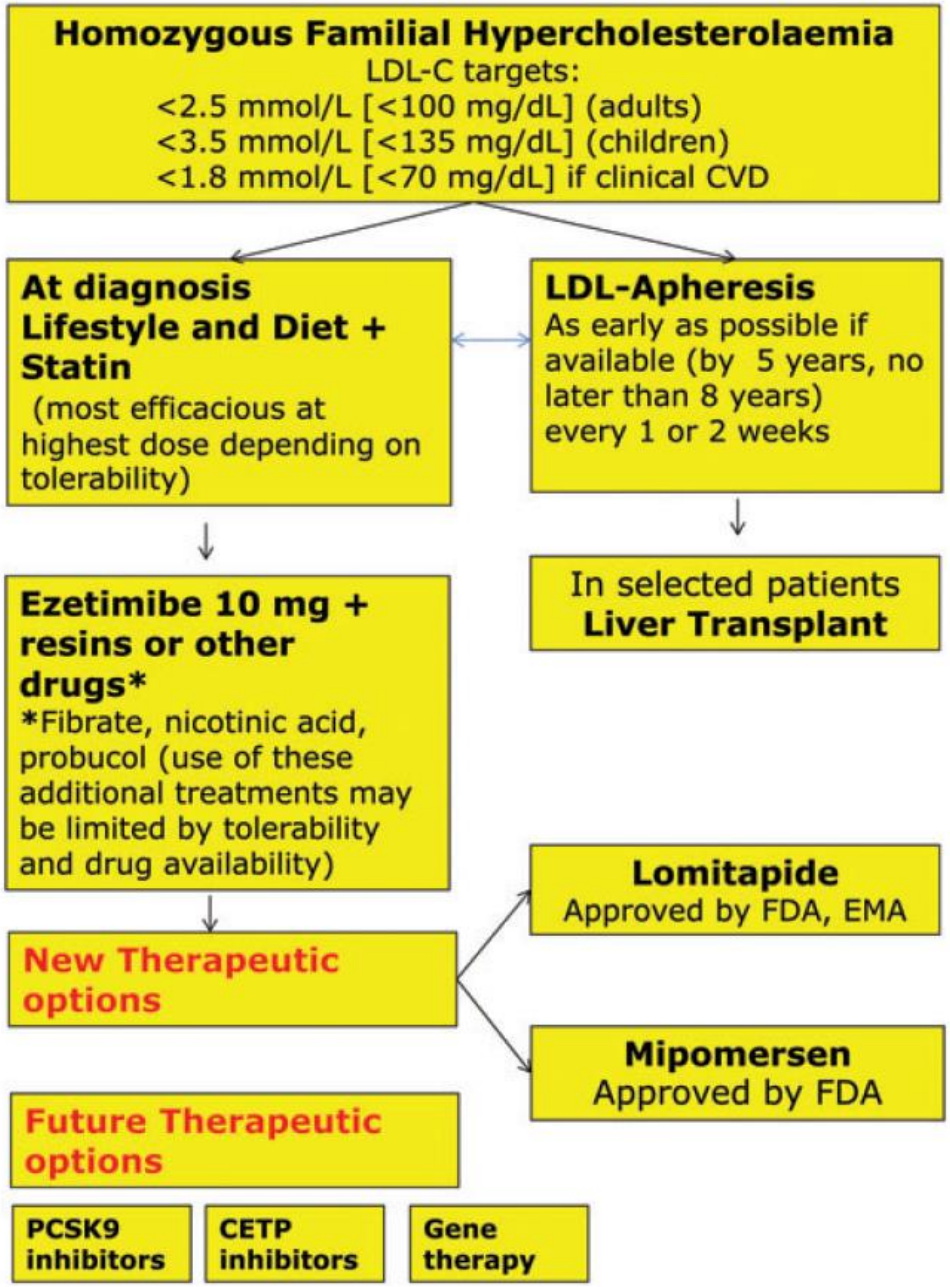
Raal et al. Lancet 2015;385:341–350.

Degradation Pathways of LDL-Receptor



Archives of Biochemistry and Biophysics 2017

Suggested algorithm for management of homozygous familial hypercholesterolaemia



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SISA: Algoritmo terapeutico per la FH omozigote

In tutti i pazienti, il prima possibile

- Raccomandazioni dietetiche e sullo stile di vita
- Statine alla massima dose tollerata
- Aggiungere ezetimibe/fibrati
- In pazienti intolleranti alle statine: sequestranti degli acidi biliari (resine a scambio ionico)/ezetimibe

***C-LDL TARGET**
< 100 mg/dL (adulti)
< 135 mg/dL (bambini)
< 70 mg/dL (se complicanze cardiovascolari)

***LDL aferesi inizio raccomandato il più precocemente possibile (entro i 5 e non oltre gli 8 anni)**

LDL aferesi settimanale/bisettimanale

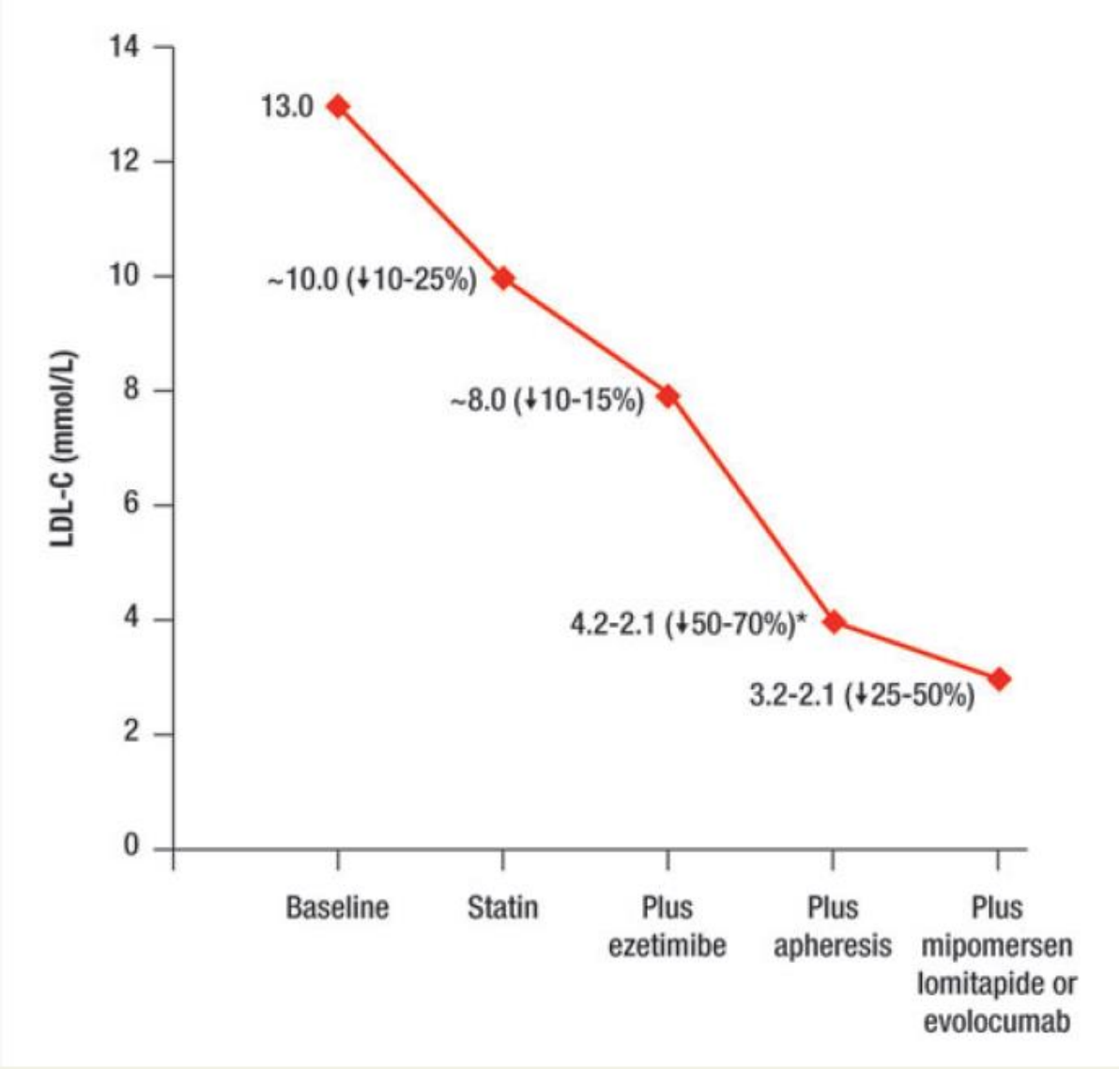
LDL aferesi non praticabile

Inibitori del PCSK9 (evolocumab)
(attività recettoriale residua)
Riduzione LDL-C attesa 25-30%

Inibizione MTP (lomitapide)
(titolare, educare il paziente)
Riduzione LDL-C attesa 50-60%

Monitorare lo stato di salute del paziente
(test funzionalità epatica, steatosi, status vascolare)

Cumulative low-density lipoprotein cholesterol lowering effects of statin, ezetimibe, adjunctive mipomersen, lomitapide or evolocumab, and lipoprotein apheresis in homozygous familial hypercholesterolaemia



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Summary of EAS Consensus Panel recommendations

- Management
  - Current management of HoFH focuses on a combination of lifestyle, statin treatment (with or without ezetimibe) and lipoprotein apheresis if available.
  - Lipid-lowering therapy should be started as early as possible.
  - Lipoprotein apheresis should be considered in all patients with HoFH, and started as soon as possible, ideally by age 5 and not later than 8 years.
  - Lomitapide and mipomersen should be considered as adjunctive treatments to further lower plasma LDL-C levels in patients with HoFH.

- Other issues
  - Contraception and pregnancy are key issues in female patients and should be appropriately discussed. Hormonal contraception is generally contraindicated in HoFH, and other contraceptive methods are strongly preferred. Women wishing to become pregnant should be counselled and undergo detailed CV assessment. Where pregnancy is not contraindicated, women should remain on LDL apheresis.
  - Psychological support should be integrated into routine care. Patient and family support groups clearly have a role.
  - Surgery may be considered to remove large cutaneous or tuberous xanthomas for either functional or cosmetic reasons

European Heart Journal 2014

HOMOZIGOUS FAMILIAL HYPERCHOLESTEROLEMIA- HoFH

DOMINANT FORM

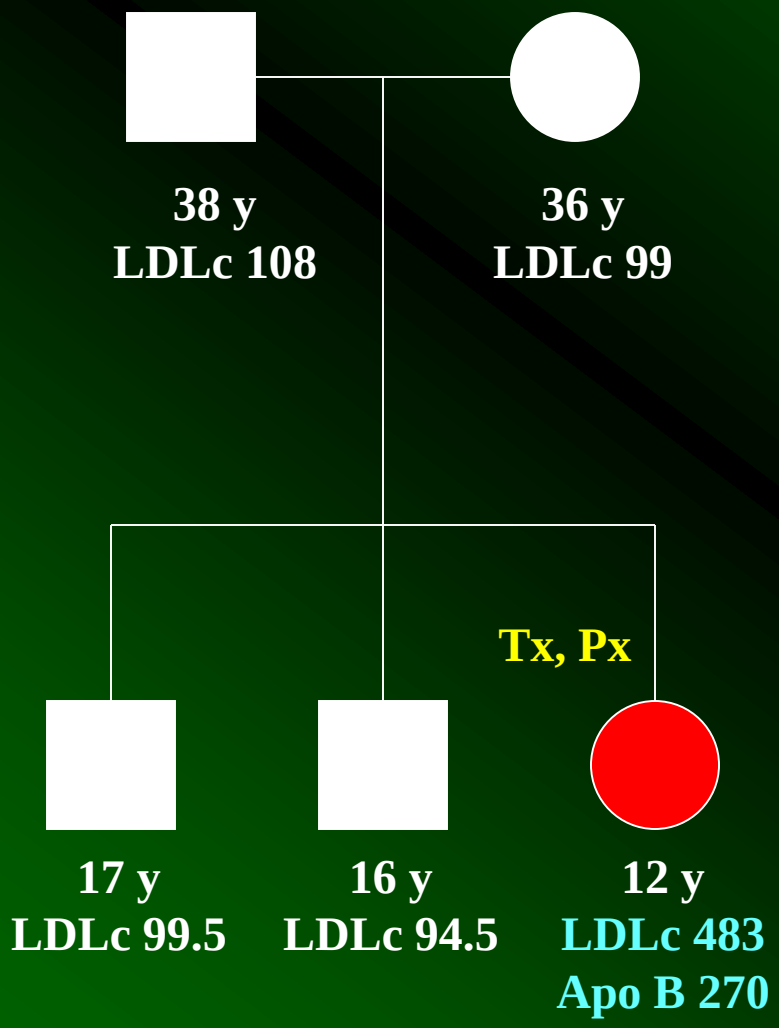
HOMOZIGOUS FAMILIAL HYPERCHOLESTEROLEMIA- HoFH

RECESSIVE FORMS

Familial hypercholesterolemia (ARH)

- Inheritable, autosomal recessive disorder
- usually due to mutations in *LDLRAP1* gene
  - ~13 mutations
  - higher prevalence of ARH in Sardinia
  - **0.7% of Sardinians are carriers of ARH1 or ARH2 mutations**
- one form: **HoFH**
- decreased clearance of LDL particles from plasma.
- severe hypercholesterolemia and lifelong accumulation of plasma LDL leading to atherosclerosis

M. Family



LDL-R activity in fibroblasts

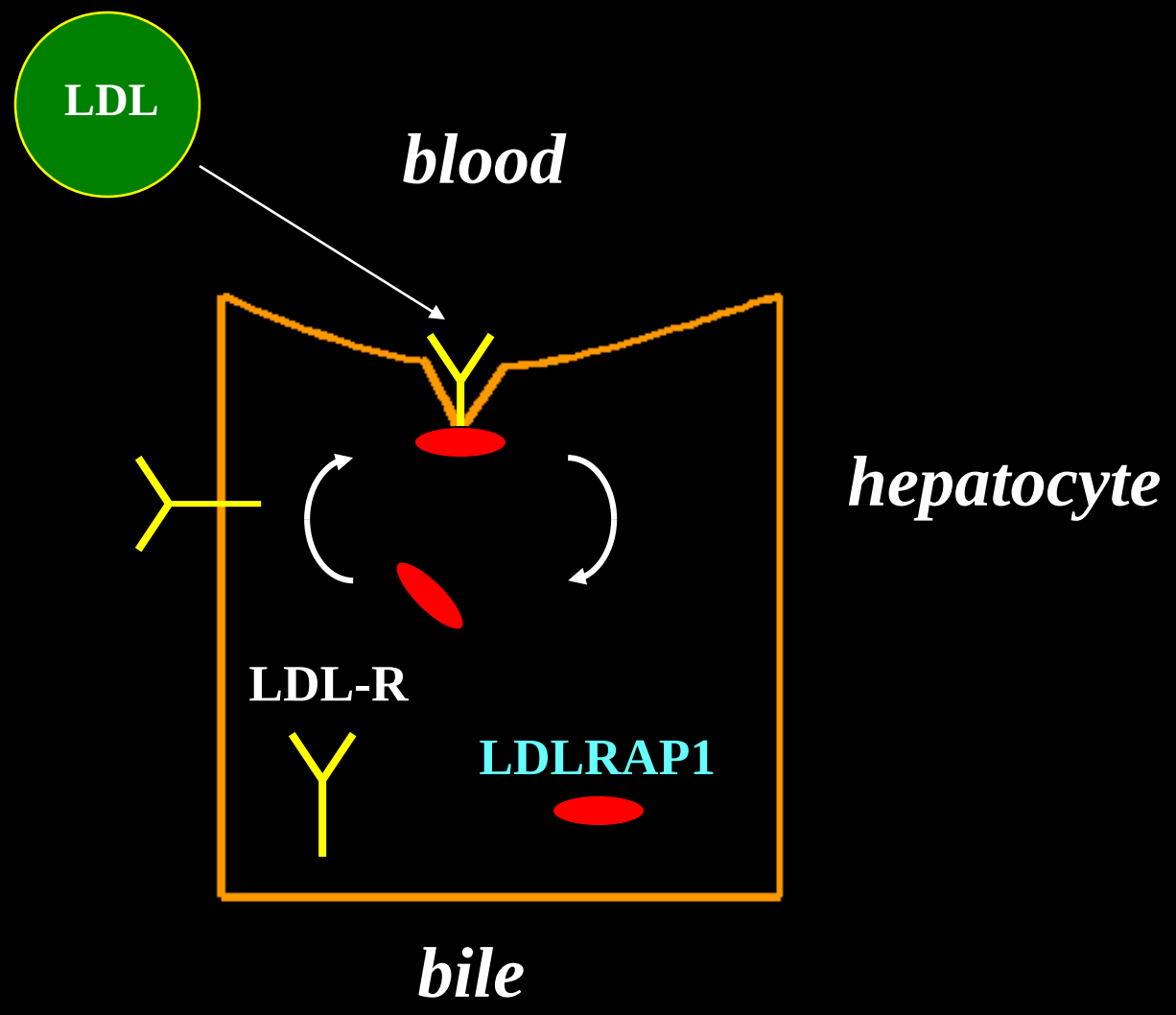
Normal

FCR of LDL-R in vivo

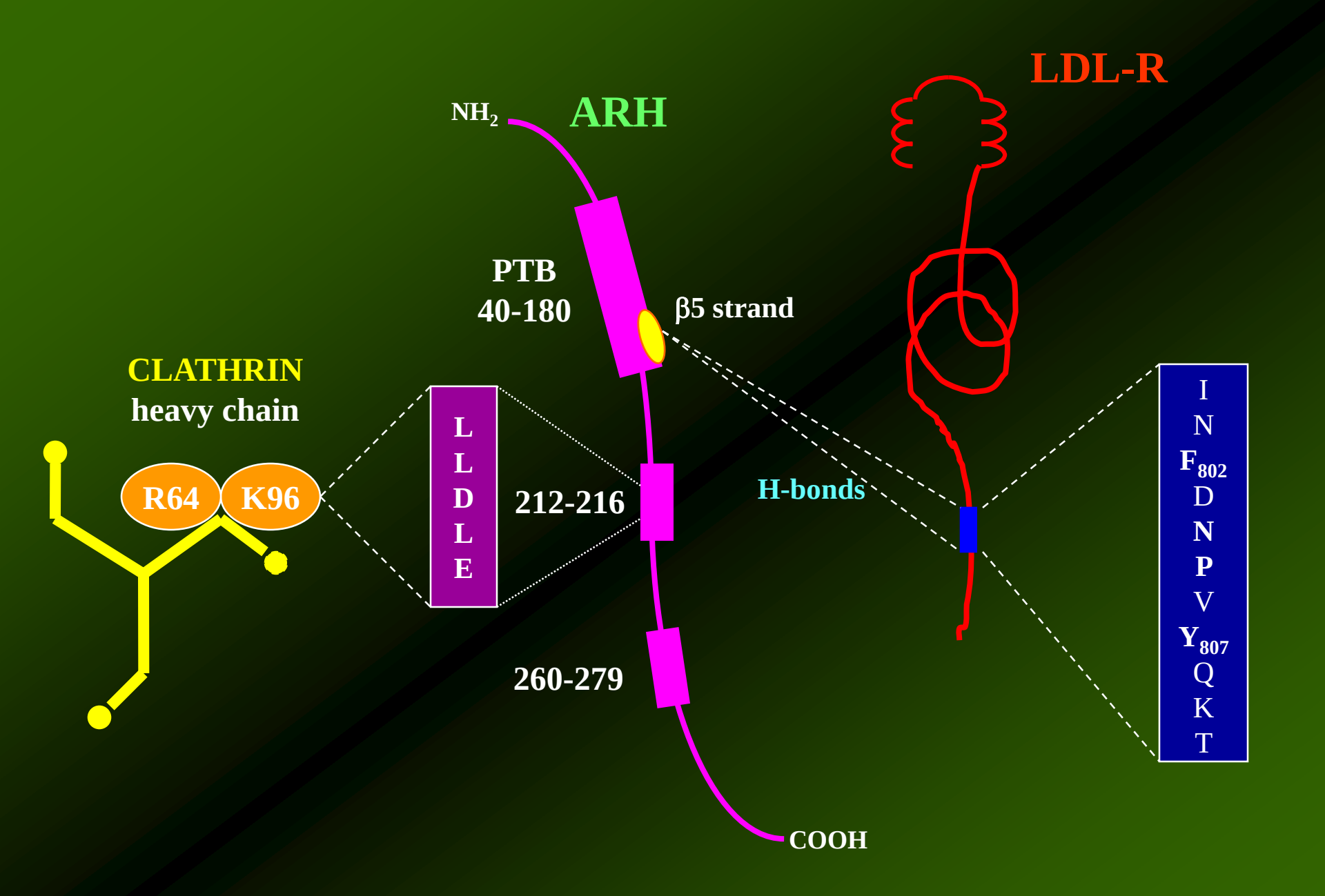
Reduced

Receptor affinity of LDL

Normal

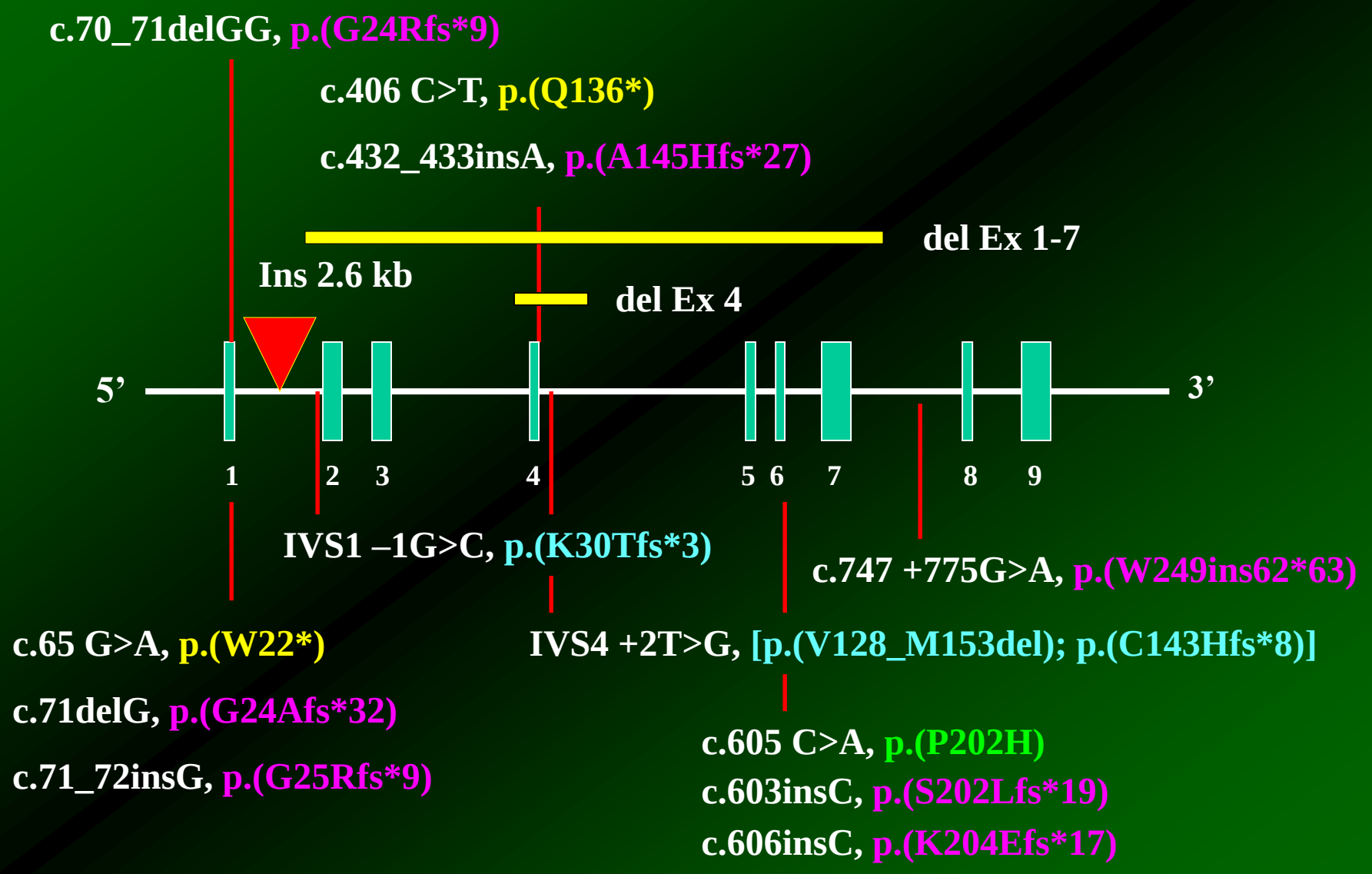


LDLRAP1: 1) stabilizes the association of LDL-R with LDL and 2) is required for the internalization of the LDL/LDL-R complex.



Dvir H et al. PNAS 2012; 109: 6916-21

LDLRAP1 gene mutations



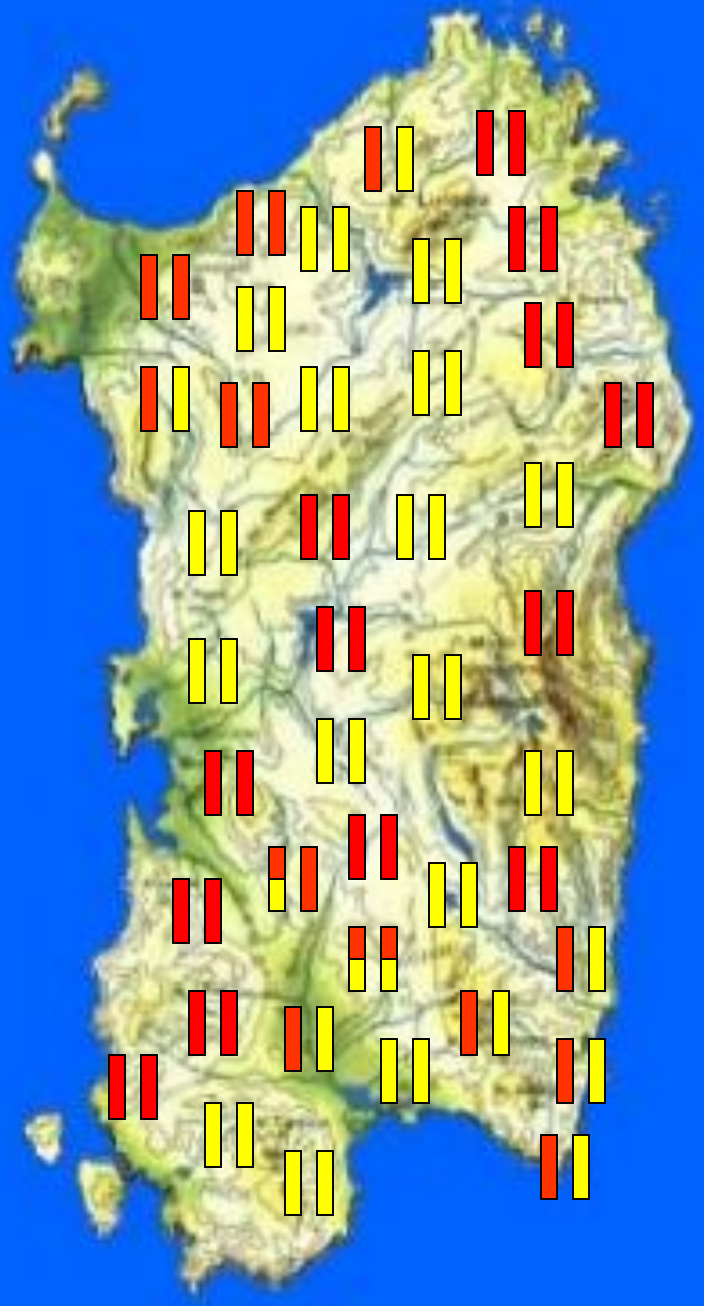
c.65 G>A, p.(W22*)

432insA, p.(A145Hfs*27)

Prevalence

Pseudohomozygotes 1:33.250

Heterozygotes 1:143



Sardinian Patients with ARH (47 from 30 families)
Sicilian Patients with ARH (2 from 1 family)

W22X W22X	n.16 (9 families); LDLc 14.2±2.5 mmol/L
432insA 432insA	n.18 (13 families); LDLc 14.8±3.2 mmol/L
W22X 432insA	n.12 (7 families); LDLc 14.2±1.9 mmol/L
432insA W22X+432insA	n.1 (1 family); LDLc 18.2 mmol/L
W22X+432insA W22X+432insA	n.2 (1 family); LDLc 13.0±0.9 mmol/L

ARH patients

	ITALY	Other Conutries	P
M/F	29/20	14/17	NS
Age (years)	32.4±14.3	20.6±15.1	0.001
BMI (Kg/m^2)	22.2±3.5	-	-
Tc (mmol/L)	16.1±2.7	15.4±2.8	NS
LDLc (mmol/L)	14.5±2.6	13.9±2.8	NS
HDLc (mmol/L)	1.14±0.21	-	-
Tg (mmol/L)	1.20±0.55	-	-

Values are mean±SD

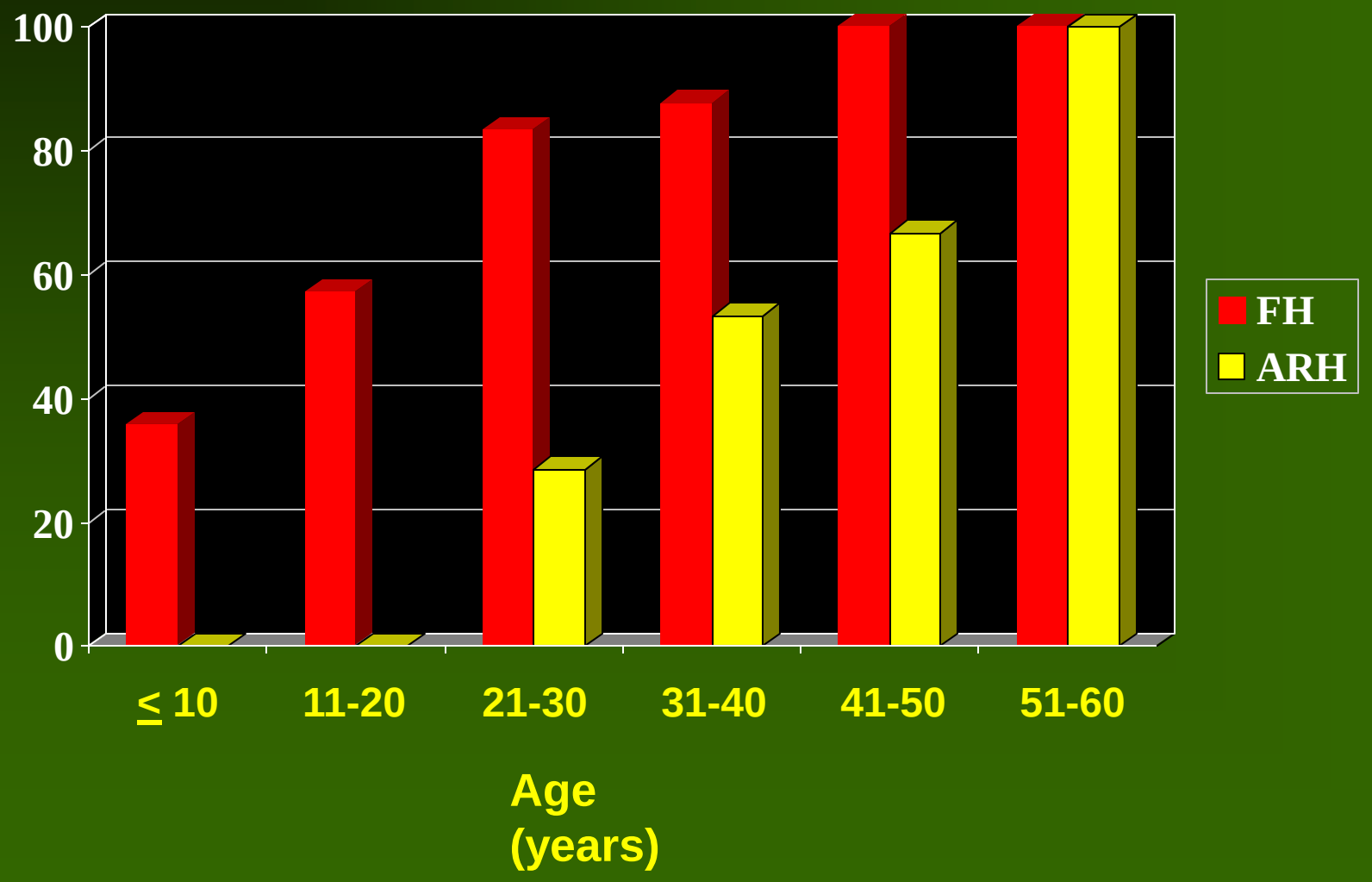
ARH Italian patients (29 M, 20 F)

	mean±SD	range	median	IQ range
Age (years)	32.4±14.3	6-69	33	21-40
BMI (Kg/m^2)	22.2±3.5	14.0-28.9	23	19.3-25.0
Tc (mmol/L)	16.1±2.7	11.6-24.2	15.9	14.2-17.1
LDLc (mmol/L)	14.5±2.6	9.6-21.6	14.3	12.5-15.4
HDLc (mmol/L)	1.14±0.21	0.70-1.94	1.16	0.98-1.25
Tg (mmol/L)	1.20±0.55	0.55-3.72	1.09	0.88-1.35

Px 55.1%, Tux 62.2%, Tx 91.8%, Ac 64.8%

Prevalence (%) of CAD in Italian ARH patients

Prevalence (%) of CAD in homozygous and compound heterozygous FH and ARH patients



Comparison between FH and ARH patients with and without CAD

	FH		ARH	
	CAD (-)	CAD (+)	CAD (-)	CAD (+)
M/F	6/9	17/12	14/11	10/7
Age (years)	11.6±2.6	29.8±2.8	24.9±2.3†	40.2±2.4*
TC (mmol/L)	18.4±0.9	18.5±0.8	16.0±0.5*	15.8±0.5*
LDLc (mmol/L)	17.1±0.9	17.0±0.8	14.3±0.5*	14.0±0.5*
HDLc (mmol/L)	0.76±0.06	0.78±0.04	1.18±0.05†	1.14±0.04†
TG (mmol/L)	1.09±0.11	1.44±0.08	0.98±0.04	1.31±0.12

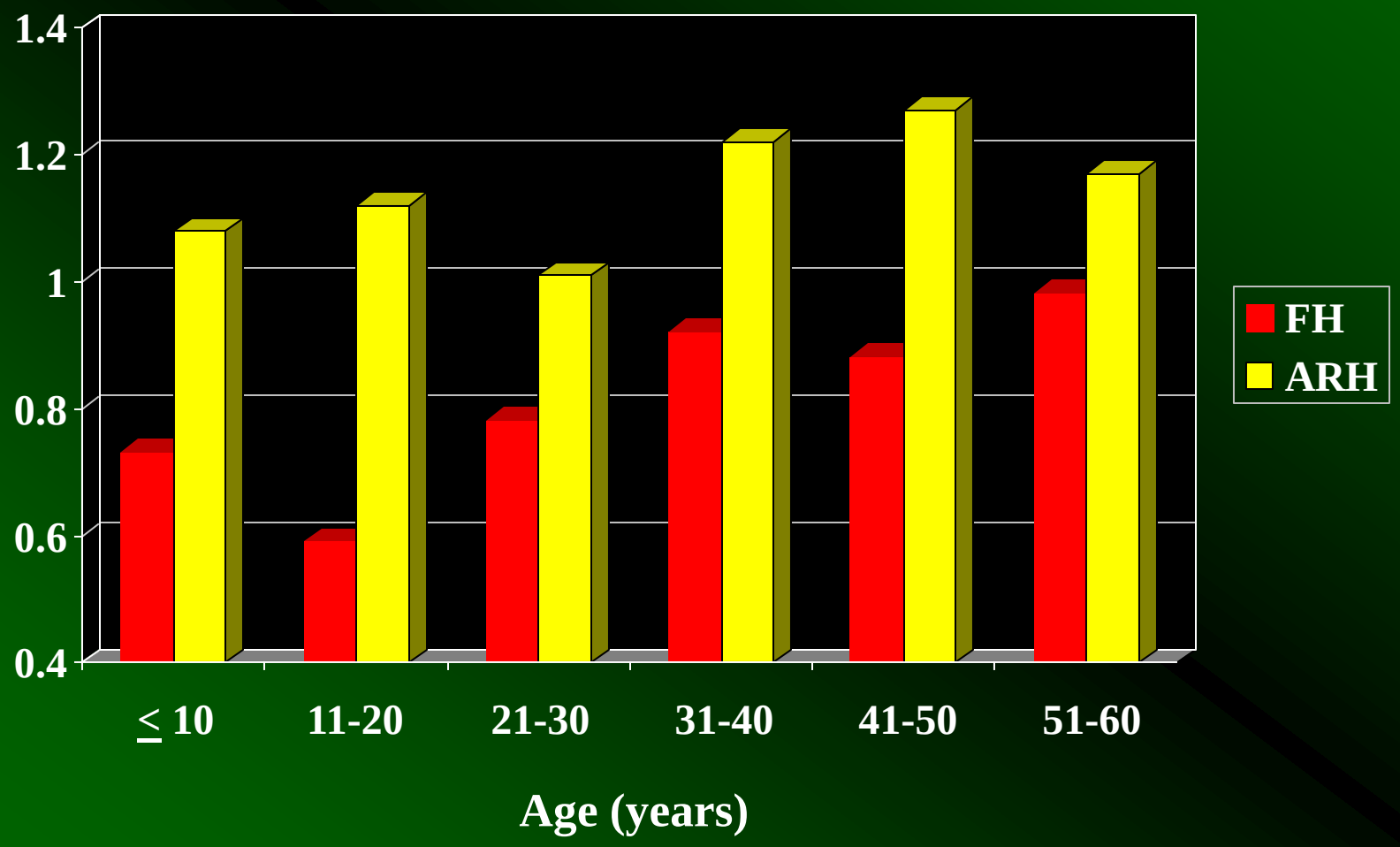
Values are M±SE; ARH vs FH *$P < 0.02$, †$P < 0.001$

Comparison between homozygous or compound heterozygous FH (NEG and DEF) and ARH patients

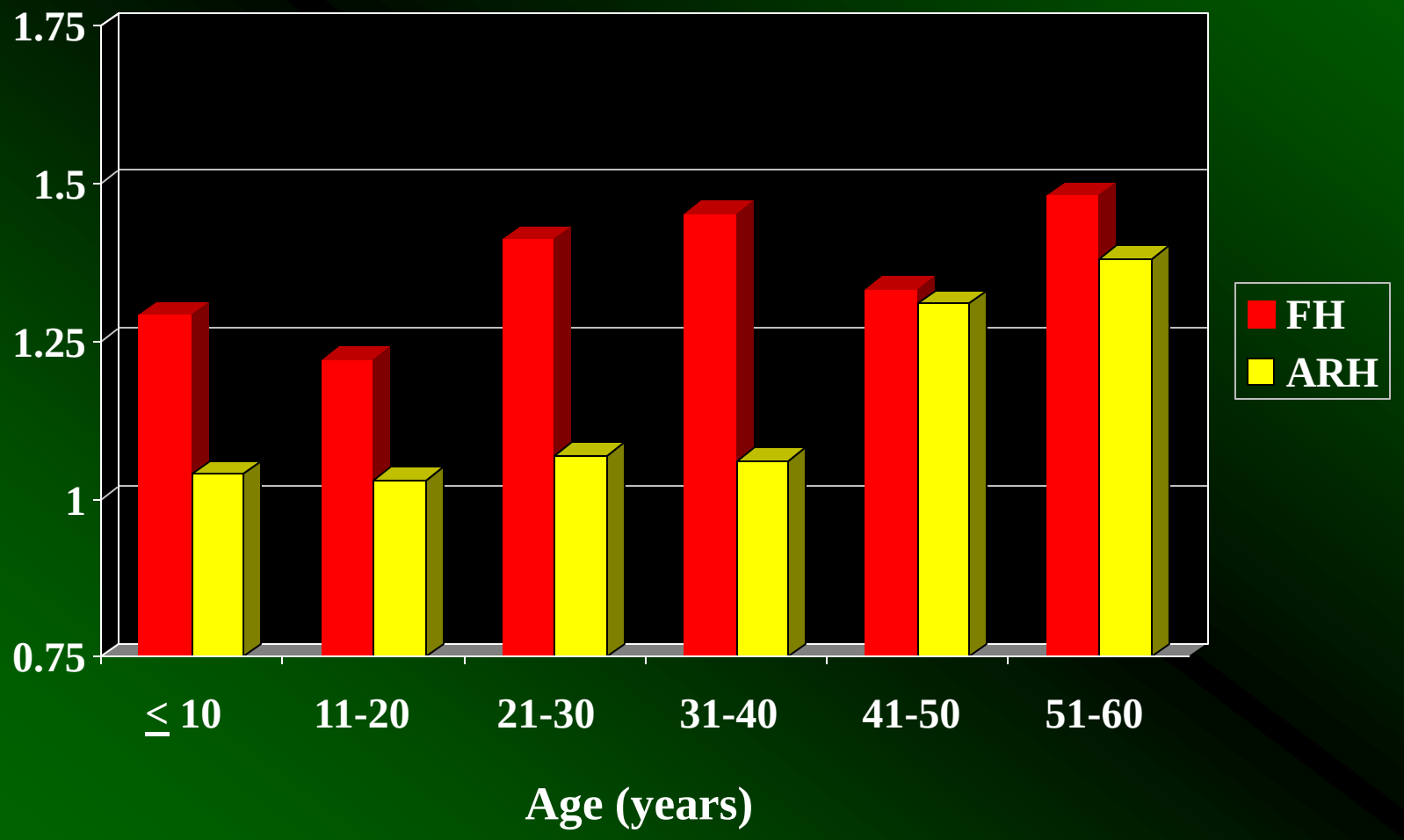
	FH-NEG	FH-DEF	ARH
N	14	26	42
Age (years)	12.8±11.8†	28.1±15.8	31.1±13.3
LDLc (mmol/L)	21.38±3.56†	15.52±2.39†	14.25±2.29
HDLc (mmol/L)	0.69±0.20†	0.82±0.21†	1.16±0.22
Tg (mmol/L)	1.43±0.42†	1.29±0.52	1.11±0.39
CAD (%)	71.4†	61.5	40.5

†Significantly different from ARH

Mean HDL cholesterol levels (mmol/L) in homozygous and compound heterozygous FH and ARH patients



Mean Triglycerides levels (mmol/L) in homozygous and compound heterozygous FH and ARH patients



HOMOZIGOUS FAMILIAL HYPERCHOLESTEROLEMIA- HoFH

DOMINANT FORM

HOMOZIGOUS FAMILIAL HYPERCHOLESTEROLEMIA- HoFH

RECESSIVE FORMS

β-SITOSTEROLEMIA

Firstly described in 1974 in two sisters with extensive tendon xanthomas and strongly increased plant sterol concentrations in plasma

Bahattacharyya AK and Connor WE J Clin Invest 1974; 53: 1033-43

β-SITOSTEROLEMIA/PHYTOSTEROLEMIA

- Autosomal recessive (prevalence < 1: 1.000.000)
- Develops in childhood
- Generalized hyperabsorption of dietary sterols, including cholesterol
- Impaired biliary excretion of sterols
- >60% of ingested sitosterol is absorbed (<8% in normal individuals)
- Hypersterolemia (mean Total sterols 318.0±149.3; Total cholesterol 244.8±114.9
- From 30-fold to 100-fold elevation of plasma concentration of plant sterols: plasma sitosterol 33.2±22.0 (n.v. 0.310 ± 0.117 mg/dl); plasma campesterol 18.7±17.6(n.v. 0.484 ± 0.188 mg/dl)

β-SITOSTEROLEMIA/PHYTOSTEROLEMIA

- Tendinous and/or tuberous xanthomas
- Xanthelasma
- Hemolytic anemia
- Macrothrombocytopenia
- Premature CAD and aortic ATS
- Arthritis and arthralgias

Plant sterols

- Sitosterol
- Campesterol
- Stigmasterol
- Avenosterol

Shell fish sterols

- Brassicasterol
- 22-dehydrocholesterol
- C-26 sterol
- 24-methylele cholesterol

Plasma levels of STEROLS in the general population

	N	mg/dl	μmol/L
Cholesterol	6975	**231.8 ± 38.7**	5990 ± 1000
Sitosterol	6975	**0.300 ± 0.117**	7.230 ± 2.819
Campesterol	6975	**0.448 ± 0.182**	11.177 ± 4.541
Stigmasterol	1733	**0.067 ± 0.060**	1.623 ± 1.453
Brassicasterol	1138	**0.028 ± 0.012**	0.702 ± 0.301
Avenosterol	205	**0.021 ± 0.010**	0.508 ± 0.242
TOTAL PS	3405	**0.864 (0.483-1.245)**	21.24 (11.878-30.596)
Cholestanol	416	0.337 ± 0.111	8.670 ± 2.855
Lathosterol	1952	0.222 ± 0.113	5.740 ± 2.922

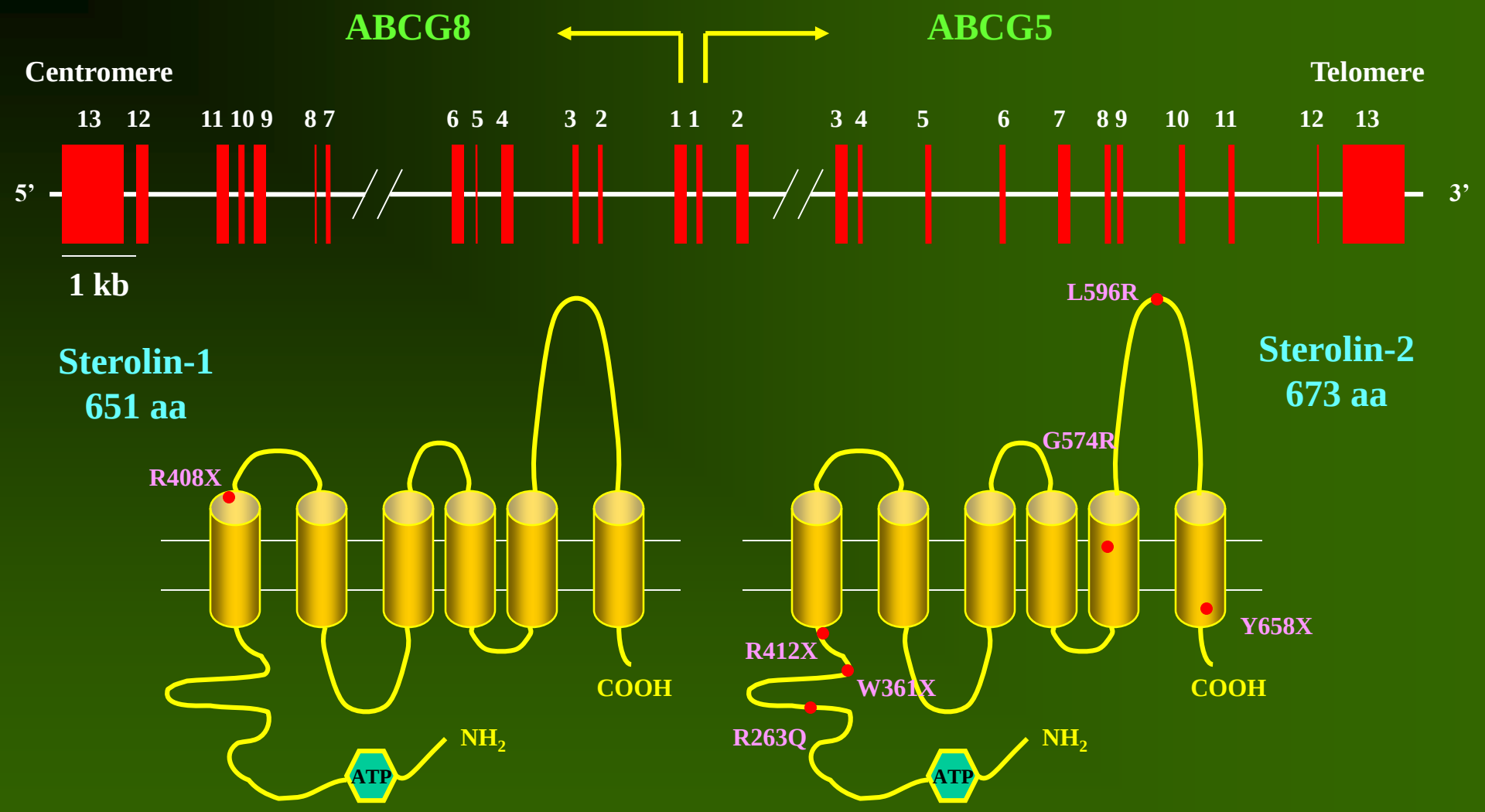
Sources of phytosterols

- Vegetable oils: Olive, Rice, Walnut, Soybean (Stigmasterol rich)
- Margarine
- Wheat germs
- Nuts, seeds
- Avocadoes
- Legumes
- Chocolate
- Shell-fish (Brassicasterol rich)

Accumulation of dietary cholesterol in sitosterolemia caused by mutations in adjacent ABC transporters.

Berge KE, Tian H, Graf GA, Yu L, Grishin NV, Schultz J, Kwiterovich P, Shan B, Barnes R, Hobbs HH

SCIENCE 2000

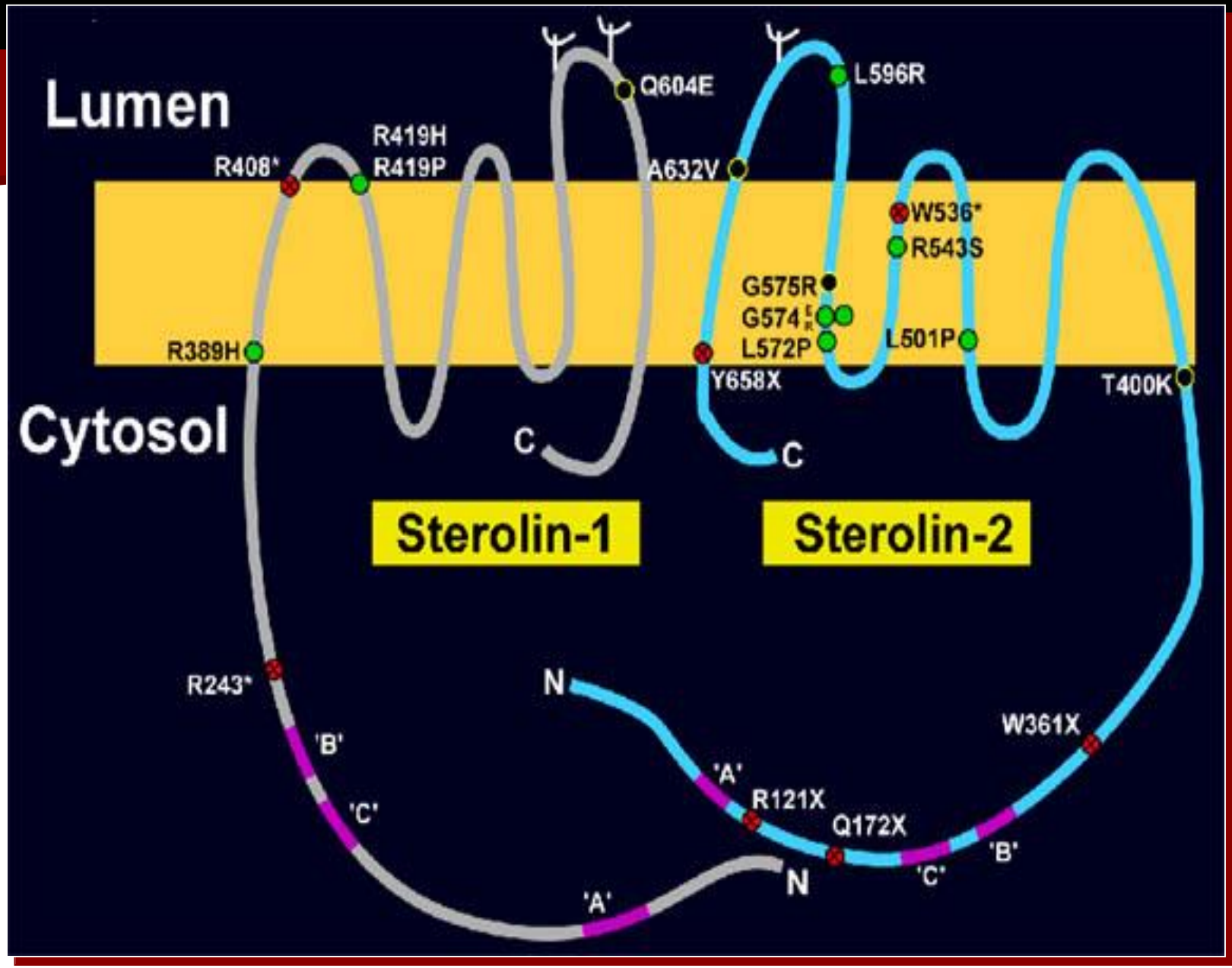


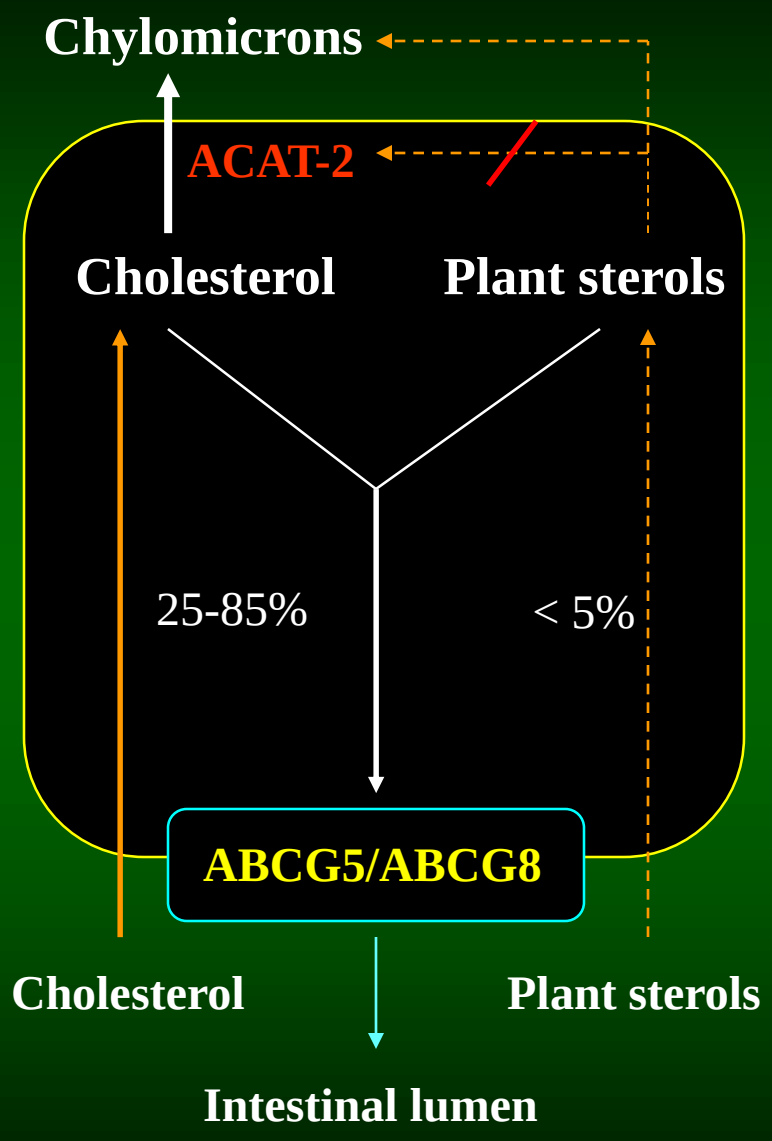
SITOSTEROLEMIA

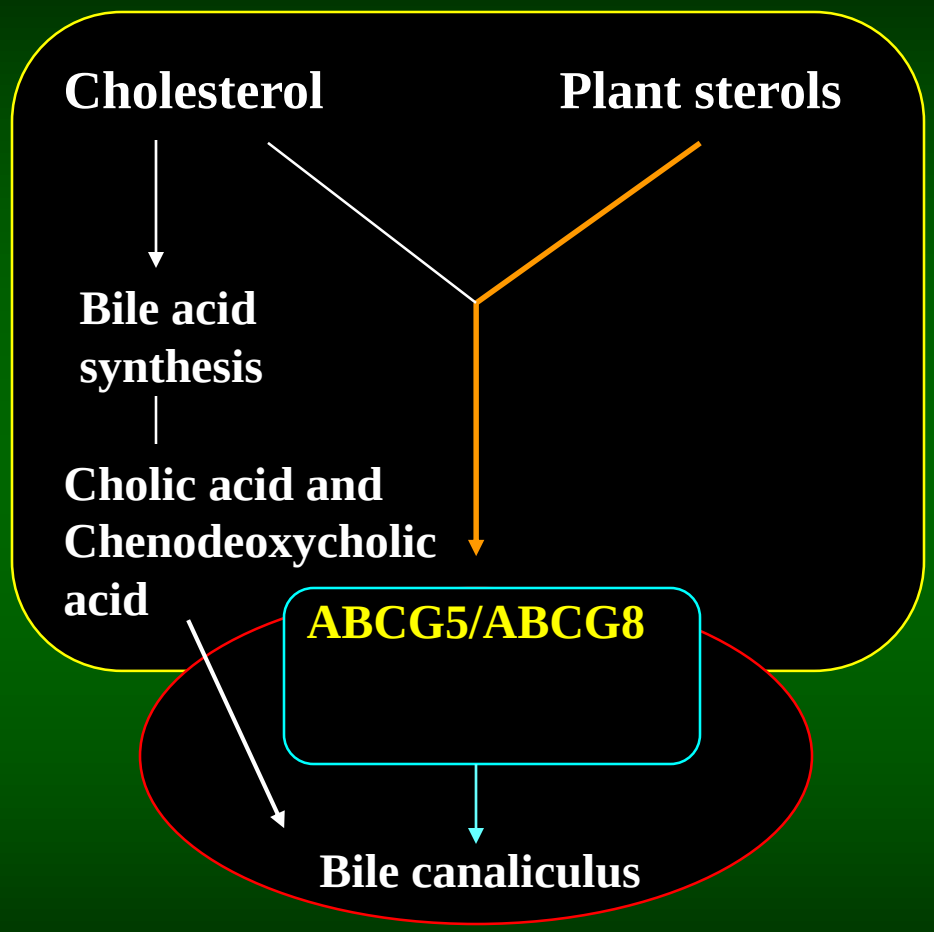
ABCG5, ABCG8 (2p21) Tendon and tuberous xanthomas, pCAD

Mean chol 258 mg/dl Mean sitosterol 35 mg/dl

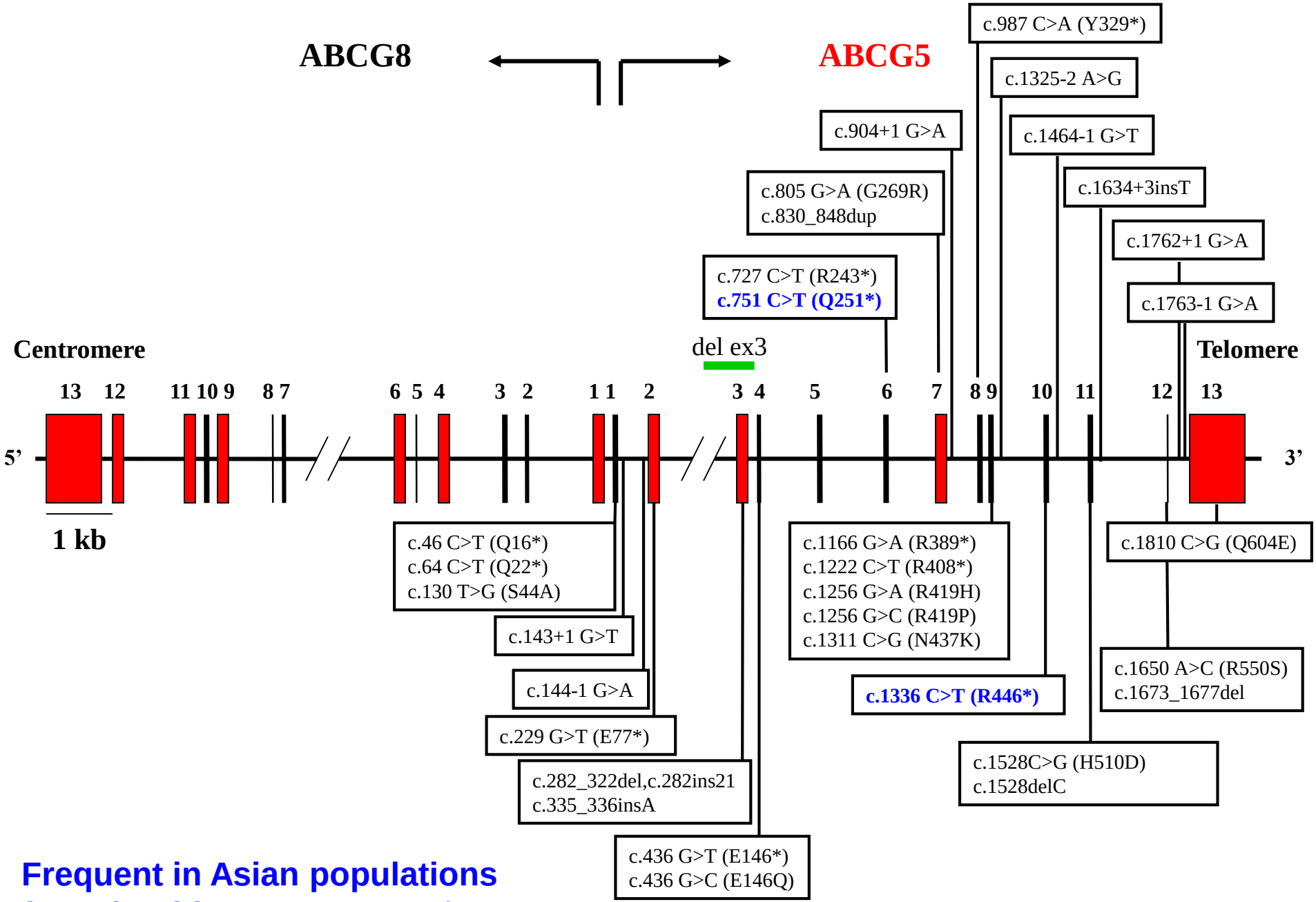
Mutations in ABCG5 and ABCG8 Cause Sitosterolemia



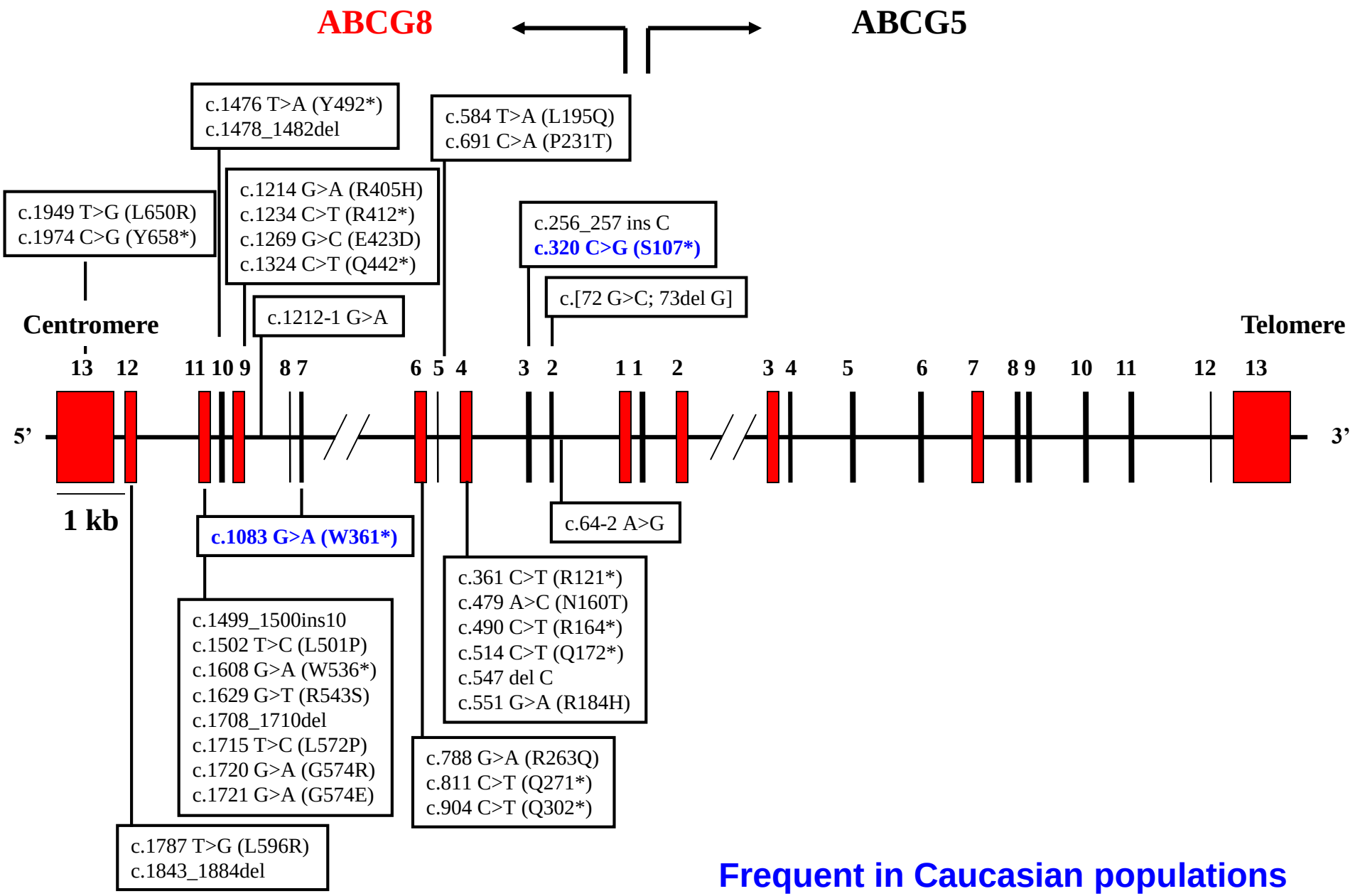




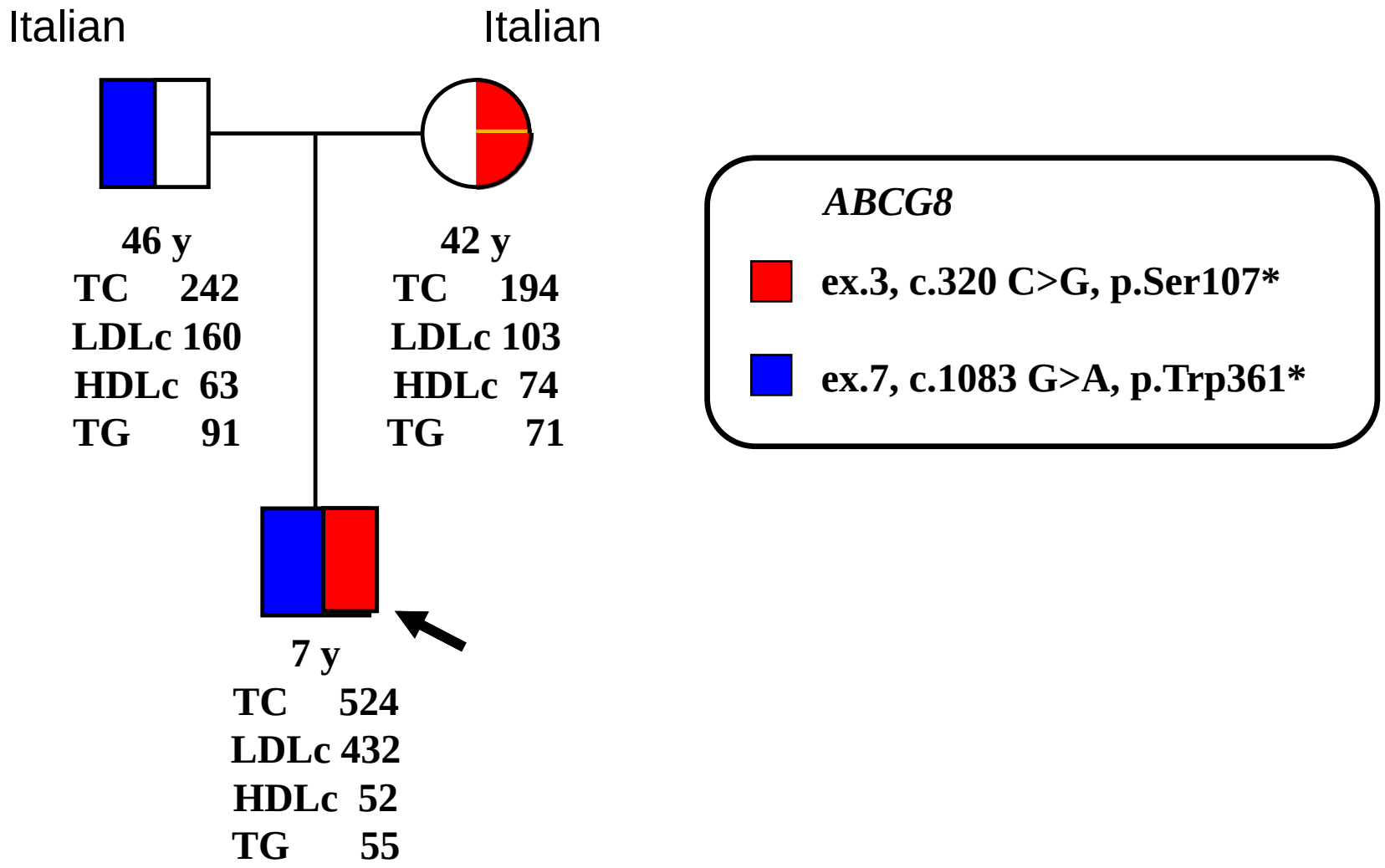
The fractional excretion of Cholesterol into the bile is much lower than that of Plant Sterols



Frequent in Asian populations (mostly Chinese, Japanese)


ABCG8
ABCG5
c.1476 T>A (Y492*)
c.1478_1482del
c.584 T>A (L195Q)
c.691 C>A (P231T)
c.1949 T>G (L650R)
c.1974 C>G (Y658*)
c.1214 G>A (R405H)
c.1234 C>T (R412*)
c.1269 G>C (E423D)
c.1324 C>T (Q442*)
c.256_257 ins C
c.320 C>G (S107*)
c.[72 G>C; 73del G]
c.1212-1 G>A
Centromere
Telomere
13 12 11 10 9 8 7 6 5 4 3 2 1 1 2 3 4 5 6 7 8 9 10 11 12 13
5'
3'
1 kb
c.1083 G>A (W361*)
c.64-2 A>G
c.361 C>T (R121*)
c.479 A>C (N160T)
c.490 C>T (R164*)
c.514 C>T (Q172*)
c.547 del C
c.551 G>A (R184H)
c.1499_1500ins10
c.1502 T>C (L501P)
c.1608 G>A (W536*)
c.1629 G>T (R543S)
c.1708_1710del
c.1715 T>C (L572P)
c.1720 G>A (G574R)
c.1721 G>A (G574E)
c.788 G>A (R263Q)
c.811 C>T (Q271*)
c.904 C>T (Q302*)
c.1787 T>G (L596R)
c.1843_1884del
Frequent in Caucasian populations

Case



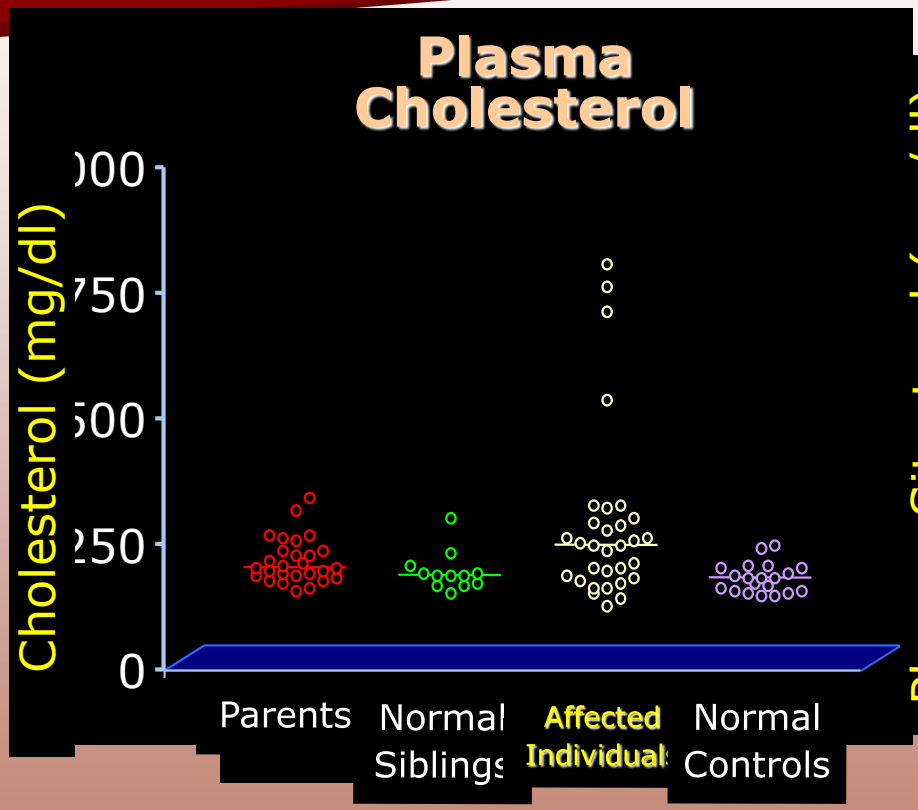
(lipid values in mg/dl)

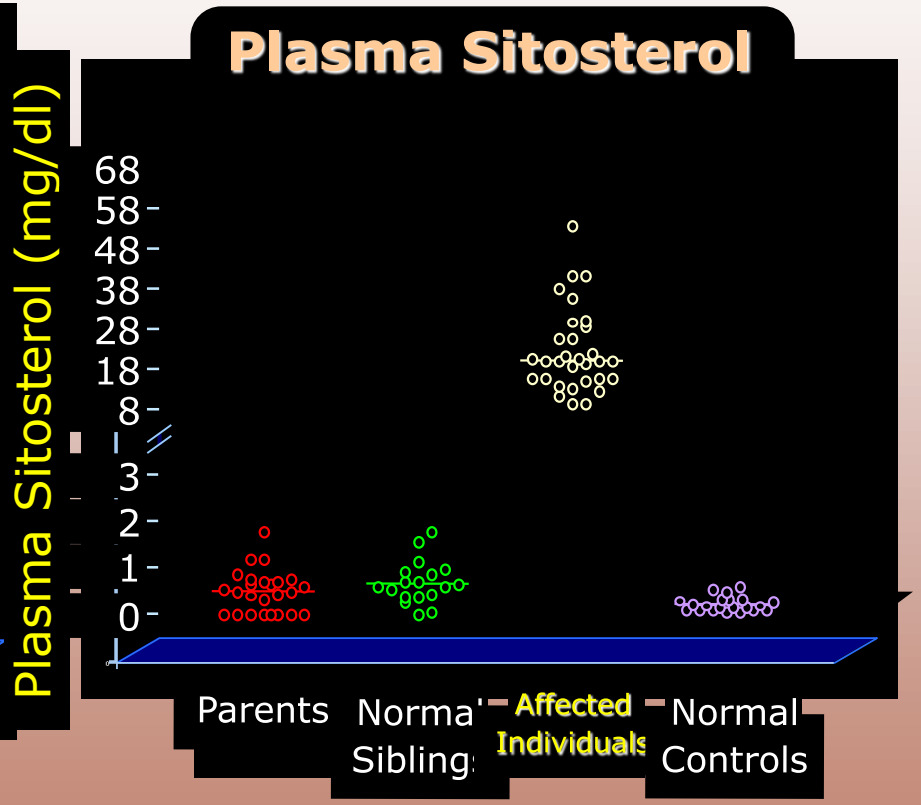
Figure 1

Sitosterolemia

- Biochemical abnormalities
  - Increased plasma phytosterols and their metabolites
  - Increased dietary cholesterol and plant sterol absorption
  - Expanded body pools of both sitosterol and cholesterol
  - Decreased ability to excrete any sterols into bile by the liver

Plasma Sitosterol and Cholesterol in Sitosterolemia





Lee MH et al. *Curr Opin Lipidol* 2001;12:141-149.

Terapia della sitosterolemia

- Dieta ipolipidica a basso contenuto di alimenti ricchi in steroli
- Ezetimibe. Ridotto assorbimento di colesterolo e steroli vegetali.
- Statine? Inibitori della sintesi del colesterolo

Take-home messages

- Sitosterolaemia is a rare genetic disease associated with high plant sterol levels; it manifests with tendon xanthomas, premature cardiovascular disease, arthralgias and occasionally unexplained haemolysis.
- ABCG5 and ABCG8 encode two half-transporters which normally expel plant sterols into the gut and biliary lumen; homozygous mutations in either one of these two genes result in impairment of normal mechanisms that keep plant sterol levels low in the human body.
- Elevated plant sterol levels in the range 25–30 mg/dl (normal $<$1 mg/dl) is pathognomonic for diagnosis of sitosterolaemia.
- The usual methods employed to estimate cholesterol levels cannot differentiate between cholesterol and plant sterols. GC–MS or HPLC are necessary to measure plant sterol levels.

HOMOZIGOUS FAMILIAL HYPERCHOLESTEROLEMIA- HoFH

DOMINANT FORM

HOMOZIGOUS FAMILIAL HYPERCHOLESTEROLEMIA- HoFH

RECESSIVE FORMS

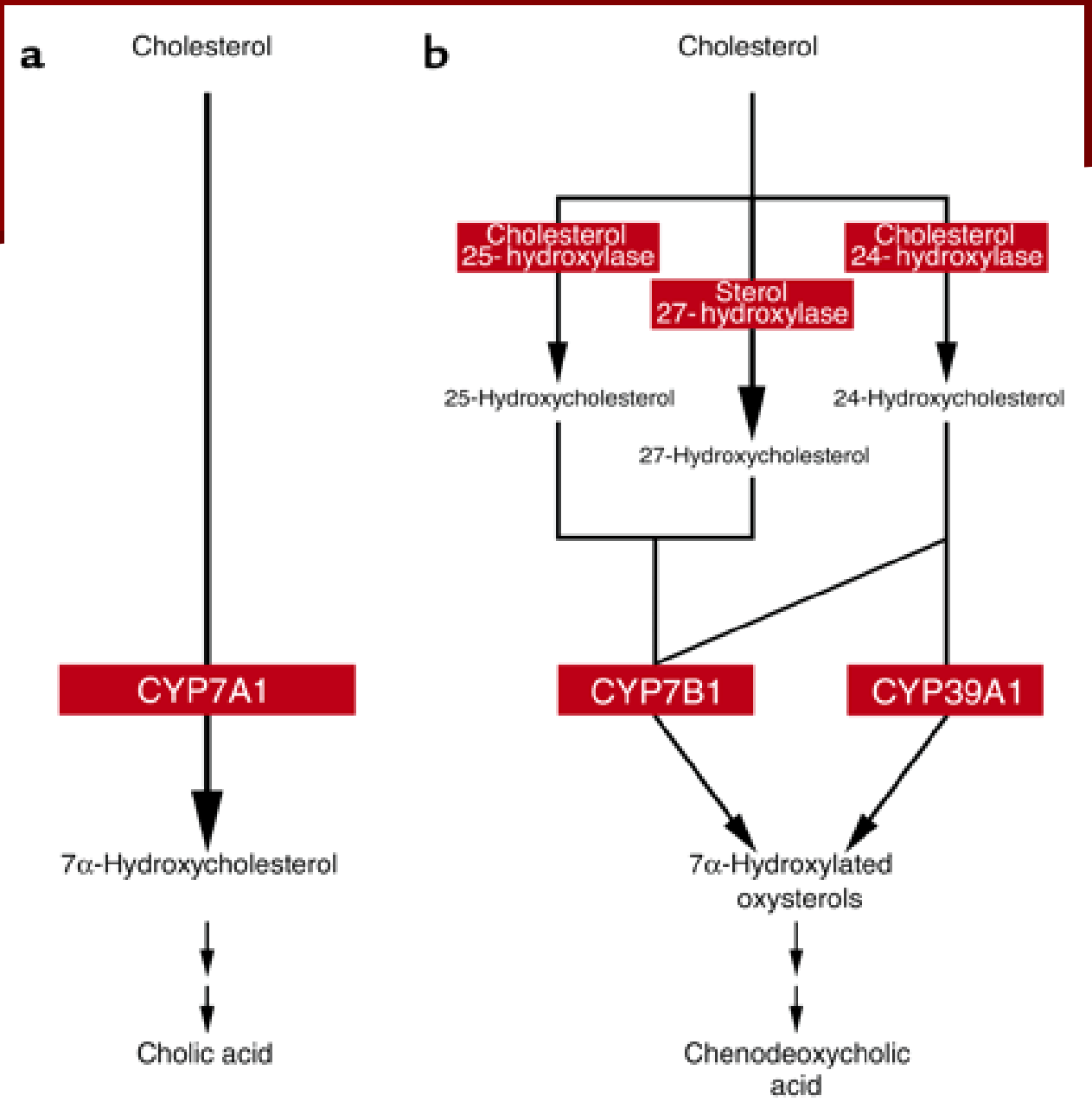
Human cholesterol 7 alpha-hydroxylase (CYP7A1) deficiency has

a hypercholesterolemic phenotype

Clive R. Pullinger, Celeste Eng, Gerald Salen, Sarah Shefer, Ashok K.Batta, Sandra K. Erickson, Andrea Verhagen, Christopher R. Rivera, Sean J. Mulvihill, Mary J. Malloy and John P. Kane1

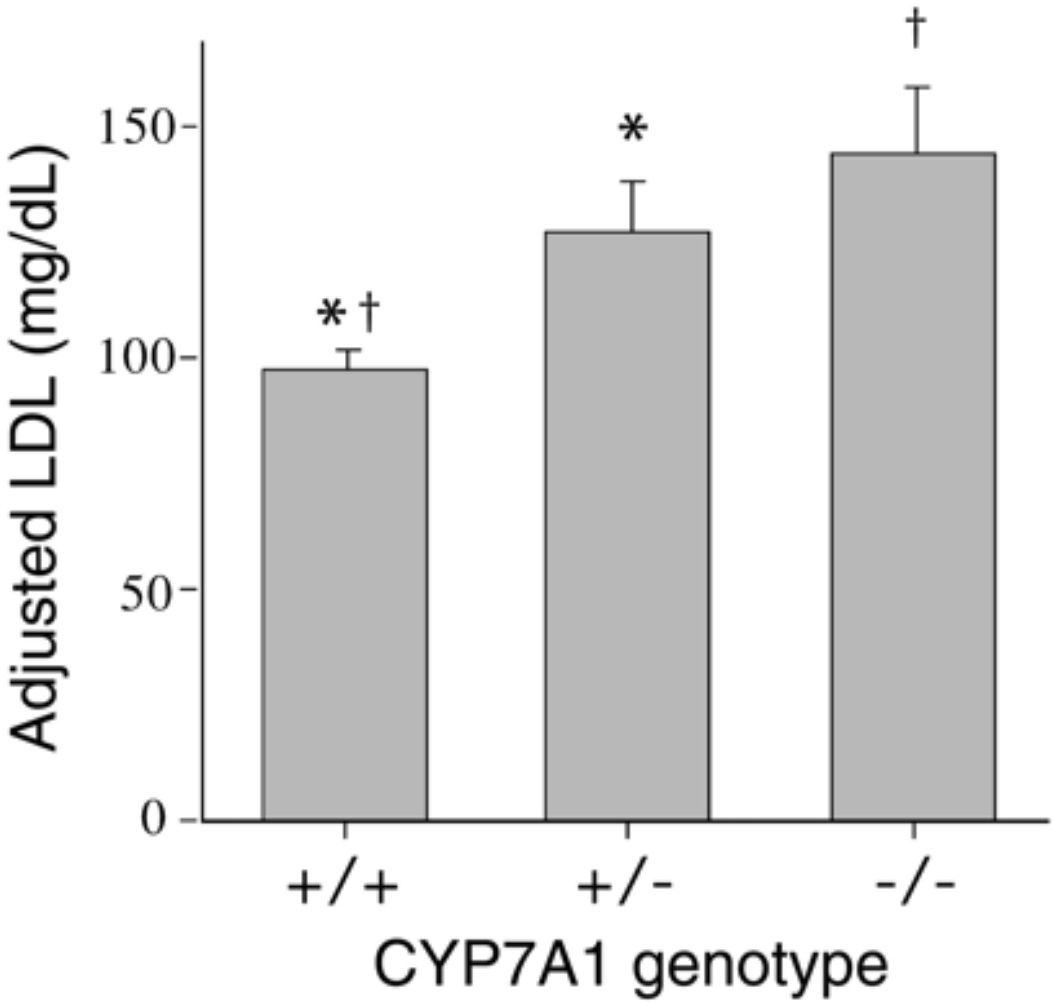
Journal of Clinical Investigation 2002

Sintesi degli acidi biliari



(a) Pathway classico
(b) Pathways alternativi

JCI, 2002

Human cholesterol 7 -hydroxylase (CYP7A1) deficiency has a hypercholesterolemic phenotype

JCI-2002