S.C. III MEDICA
SERVIZIO di DIABETOLOGIA &
MALATTIE METABOLICHE

AZIENDA OSPEDALIERO-UNIVERSITARIA
OSPEDALE di CATTINARA - TRIESTE

XII SESSIONE
AFERESI & ENDOTELIO

Inquadramento delle Malattie Dismetaboliche

Luigi Cattin

SIdEM
Società Italiana di Emaferesi e Manipolazione Cellulare

XV CONGRESSO NAZIONALE DELLA SOCIETA' ITALIANA DI EMAFERESI E MANIPOLAZIONE CELLULARE

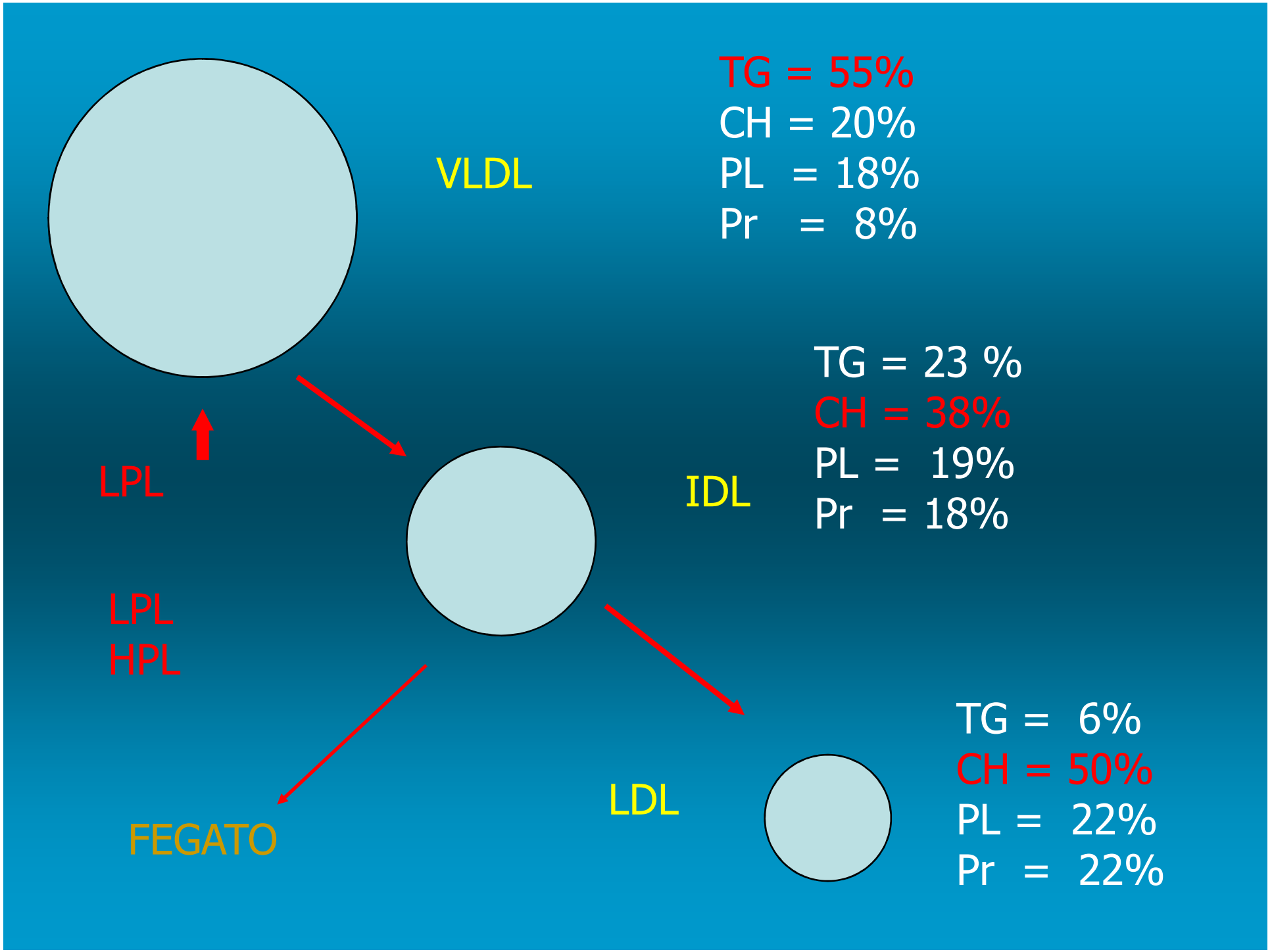
XVI CORSO DI AGGIORNAMENTO IN EMAFERESI PER PERSONALE INFERMIERISTICO E TECNICO

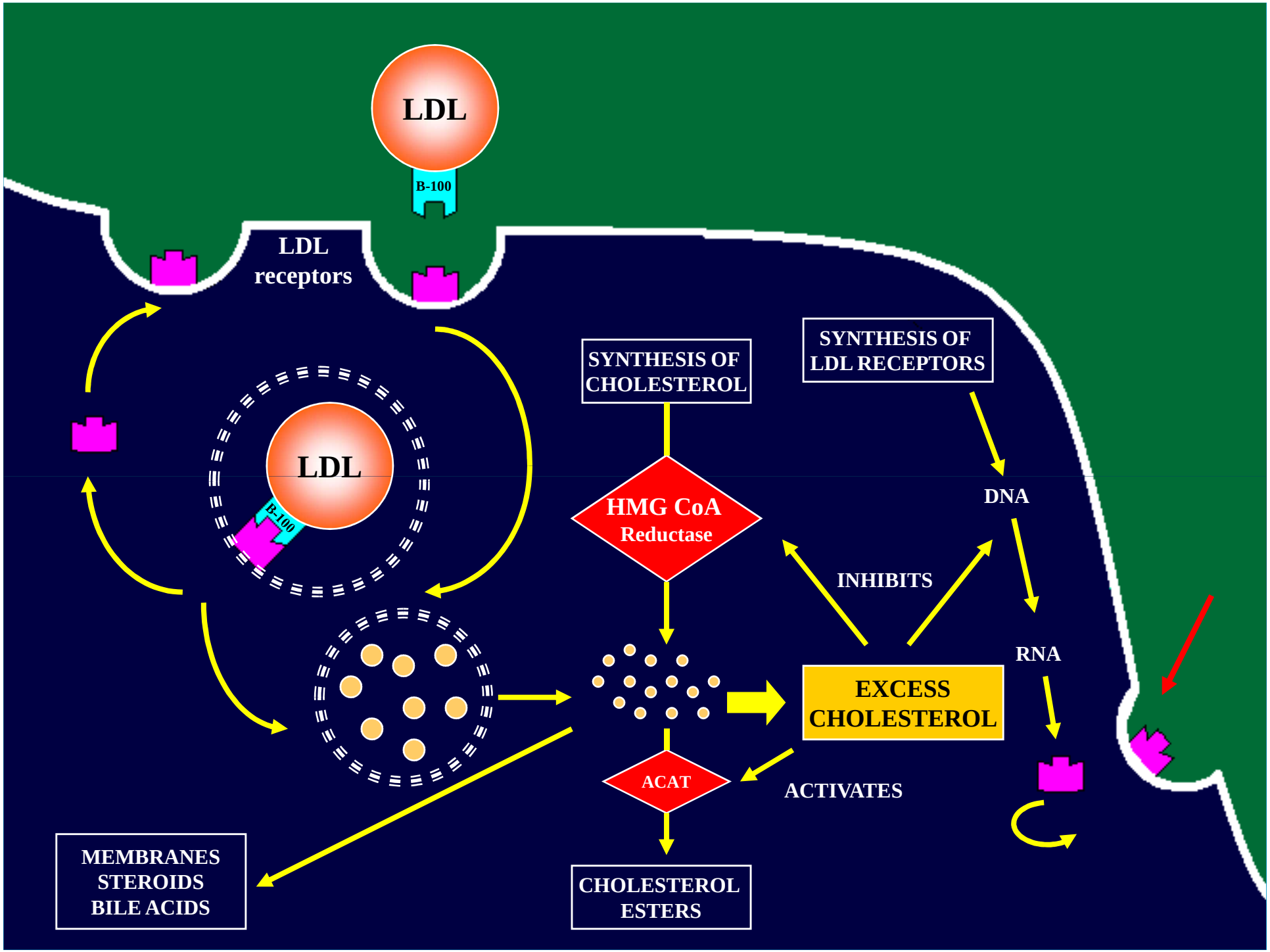
3° SIMPOSIO "CELLULE STAMINALI: DALLA BIOLOGIA ALLA CLINICA"

Torino, 9-12 novembre 2011
Centro Congressi Lingotto

The Number of Familial Dyslipidaemias in Italy

• Familial hypercholesterolemias	230.000
• *Familial combined hyperlipidemia*	> *600.000*
• Type III hyperlipidemia	10.000 ?
• Severe hypertriglyceridemias	200 ?
• *Familial hypertriglyceridemias*	*?*
• Familial hypobetalipoproteinemias	20.000
• Combined hypolipidemia	?
• Abeta & Chylomicron Retention Disease	50-100
• Familial hypoalphalipoproteinemias	?
• Familial hyperalphalipoproteinemias	?


TG = 55%
CH = 20%
PL = 18%
Pr = 8%
VLDL
LPL
TG = 23 %
CH = 38%
PL = 19%
Pr = 18%
IDL
LPL
HPL
TG = 6%
CH = 50%
PL = 22%
Pr = 22%
LDL
FEGATO


LDL
B-100
LDL receptors
LDL
B-100
SYNTHESIS OF CHOLESTEROL
SYNTHESIS OF LDL RECEPTORS
HMG CoA Reductase
DNA
INHIBITS
RNA
EXCESS CHOLESTEROL
ACAT
ACTIVATES
MEMBRANES STEROIDS BILE ACIDS
CHOLESTEROL ESTERS

INHERITED MONOGENIC HYPERCHOLESTEROLEMIAS

- Genetic disorders due to mutations of a single gene (monogenic / Mendelian disease)

- Biochemical phenotype: LDL-C >95th percentile

- Clinical phenotype:
  - Tendon and cutaneous xanthomatosis
  - Premature coronary artery disease (pCAD)

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)

DOMINANT HYPERCHOLESTEROLEMIAS

(Familial hypercholesterolemia phenotype)

Disease	Gene	Prevalence in population
FH-1 (Classic FH) Heterozygous Homozygous	LDL-R	 1 per 500 1 per million
FH-2 (FDB) Heterozygous Homozygous	Apo B-100	 1 per 1000 >1 per million
FH-3 (ADH) Heterozygous Homozygous	PCSK9	 ? ?

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FH-3 (ADH) Heterozygous Homozygous	PCSK9	 ? ?

“DOMAINS”

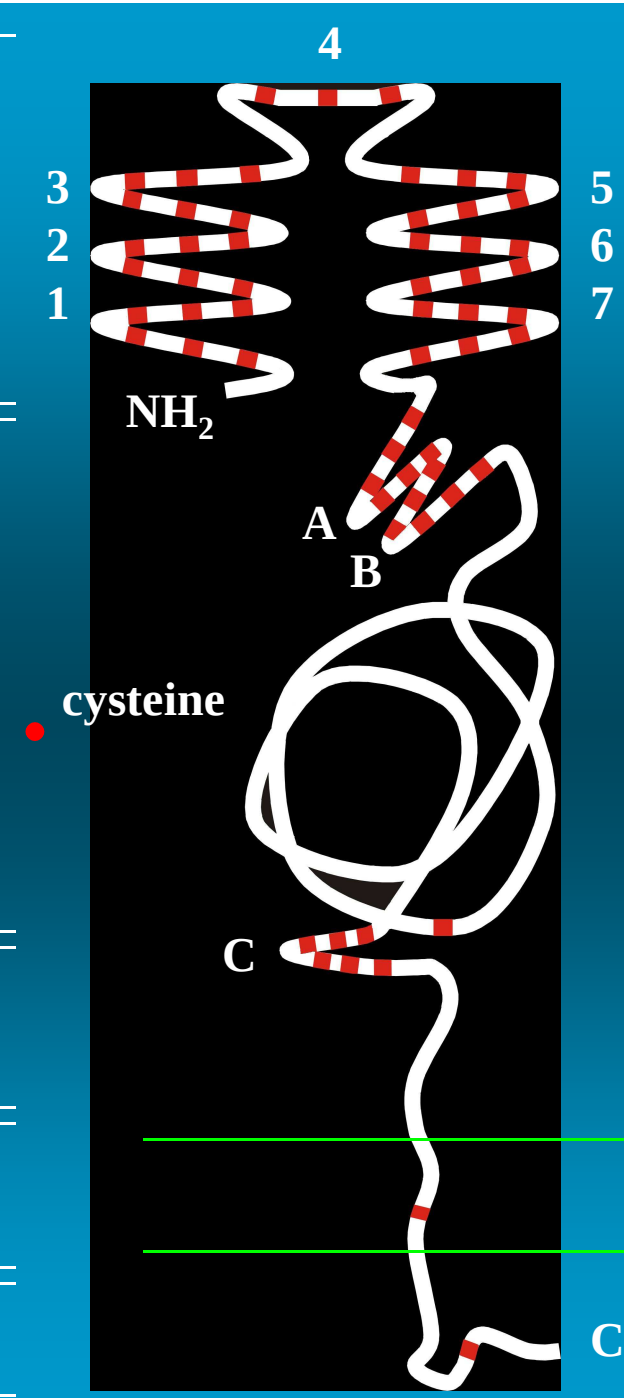
“Ligand binding”
292 aa

“ EGF precursor homology”
400 aa

“O-linked sugars”
58 aa

“Membrane spanning”
22 aa

“Cytoplasmic”
50 aa



FH in Italy

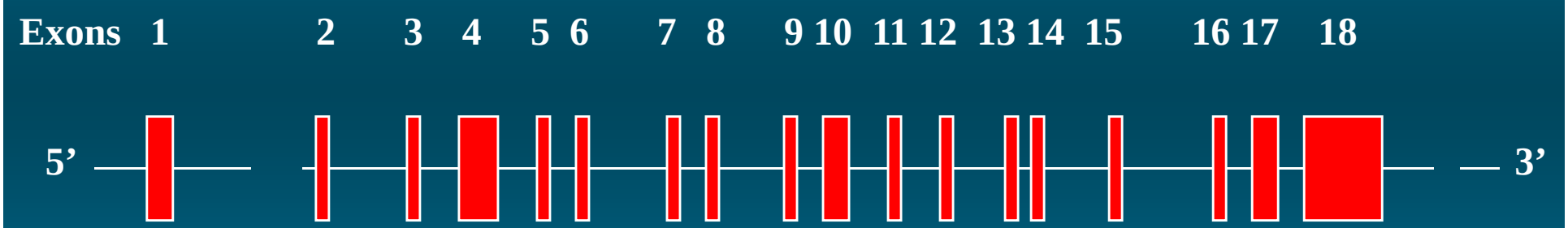
Heterozygotes n. 120.000

LDL chol. 240-450 mg/dl

Homozygotes and Compound Heterozygotes n. 50

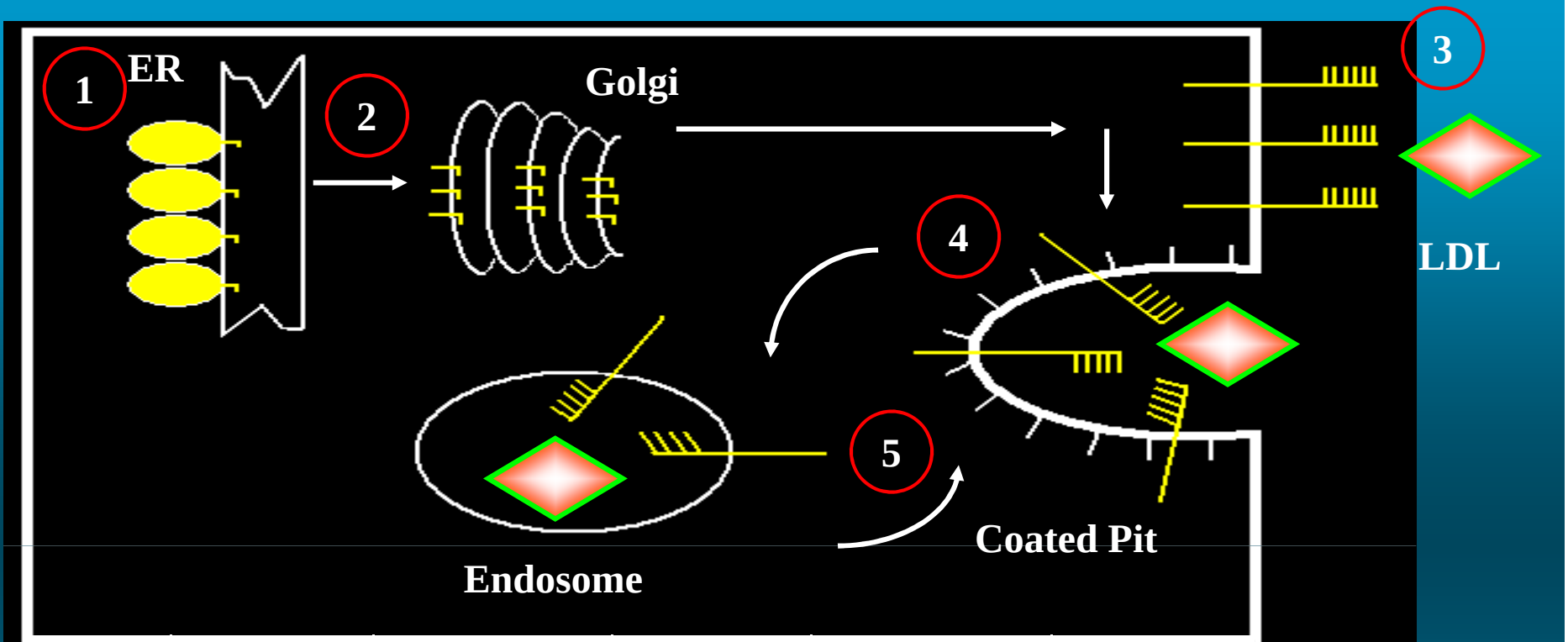
LDL chol. 420-950 mg/dl

LDL receptor gene (chr. 19p13)



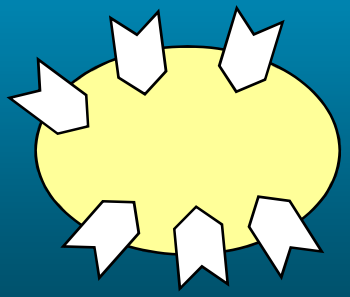
MUTATIONS OF LDL-R GENE IN ITALIAN FH-1 PATIENTS

Major Rearrangements	17
Minute Deletions/Insertion	17
Point Mutations	
Coding sequence	
Deletions/insertions	7
Missense	63
Nonsense	14
Splice junctions	13
TOTAL	131



Class	Synthesis	Transport	Binding	Clustering	Recycling
1	X				
2	→	X			
3	→	→	X		
4	→	→	→	X	
5	→	→	→	→	X

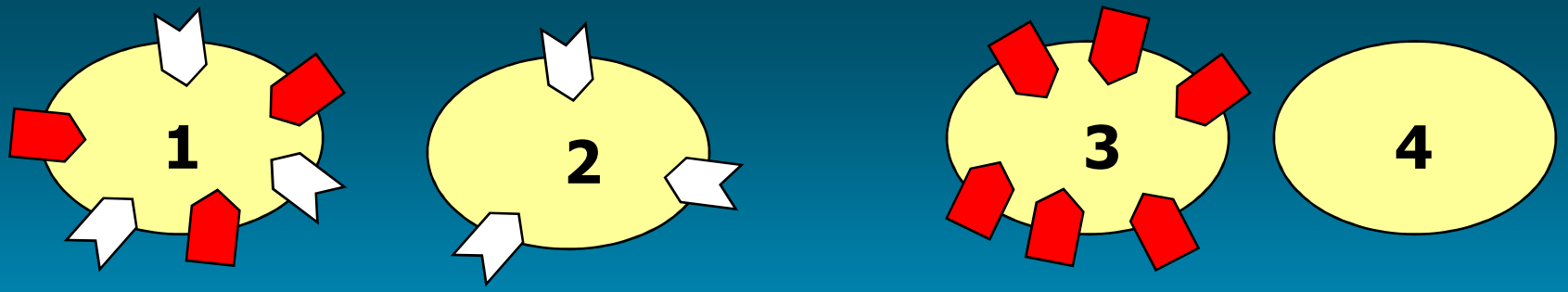
Normale



LDL-R

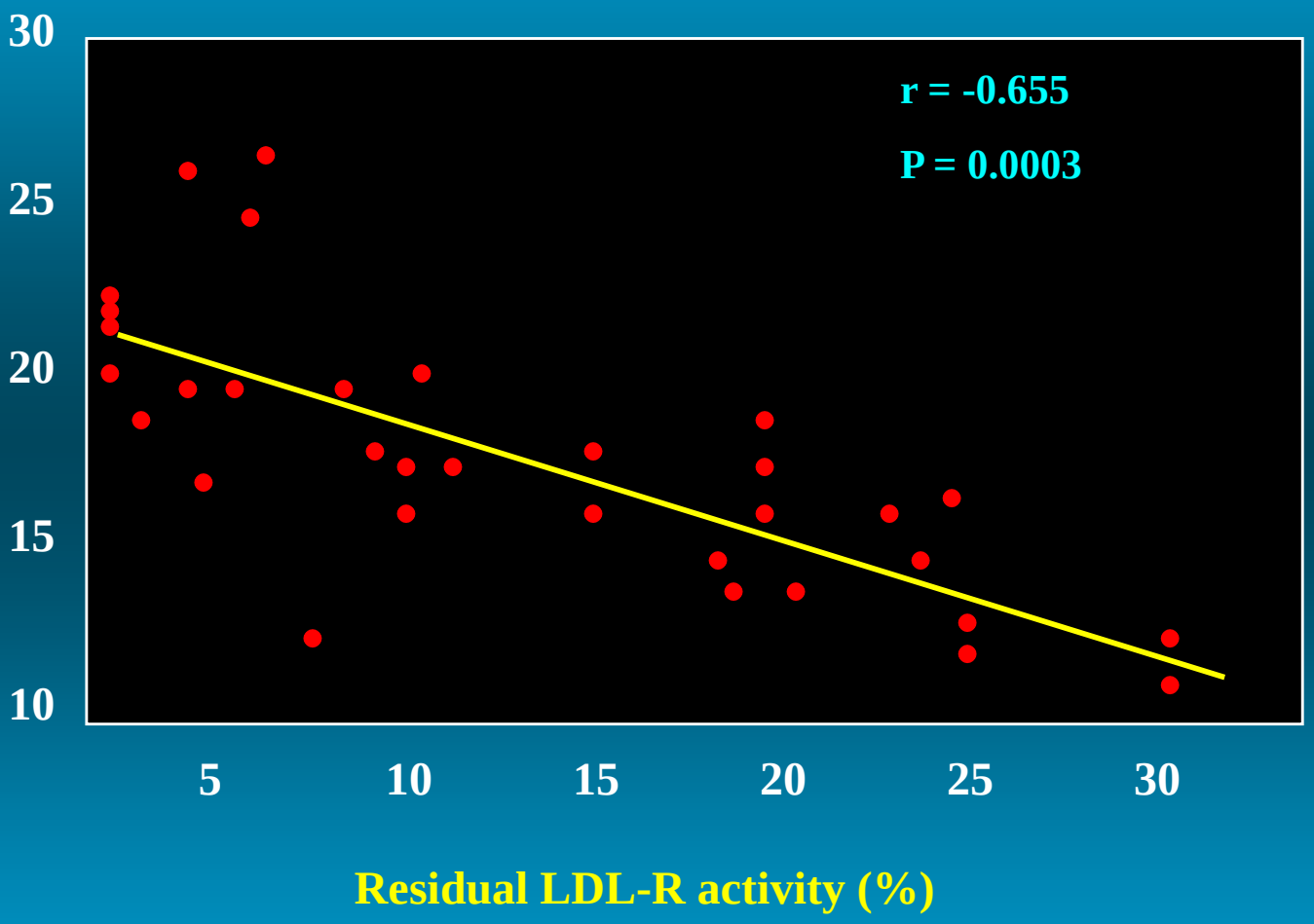
FH- eterozigote

FH- omozigote



1 e 3 Fenotipo RECETTORE-DIFETTIVO

2 e 4 Fenotipo RECETTORE-NEGATIVO


LDL-CH (mmol/L)
30
25
20
15
10
r = -0.655
P = 0.0003
5
10
15
20
25
30
Residual LDL-R activity (%)

DOMINANT HYPERCHOLESTEROLEMIAS
(Familial hypercholesterolemia phenotype)

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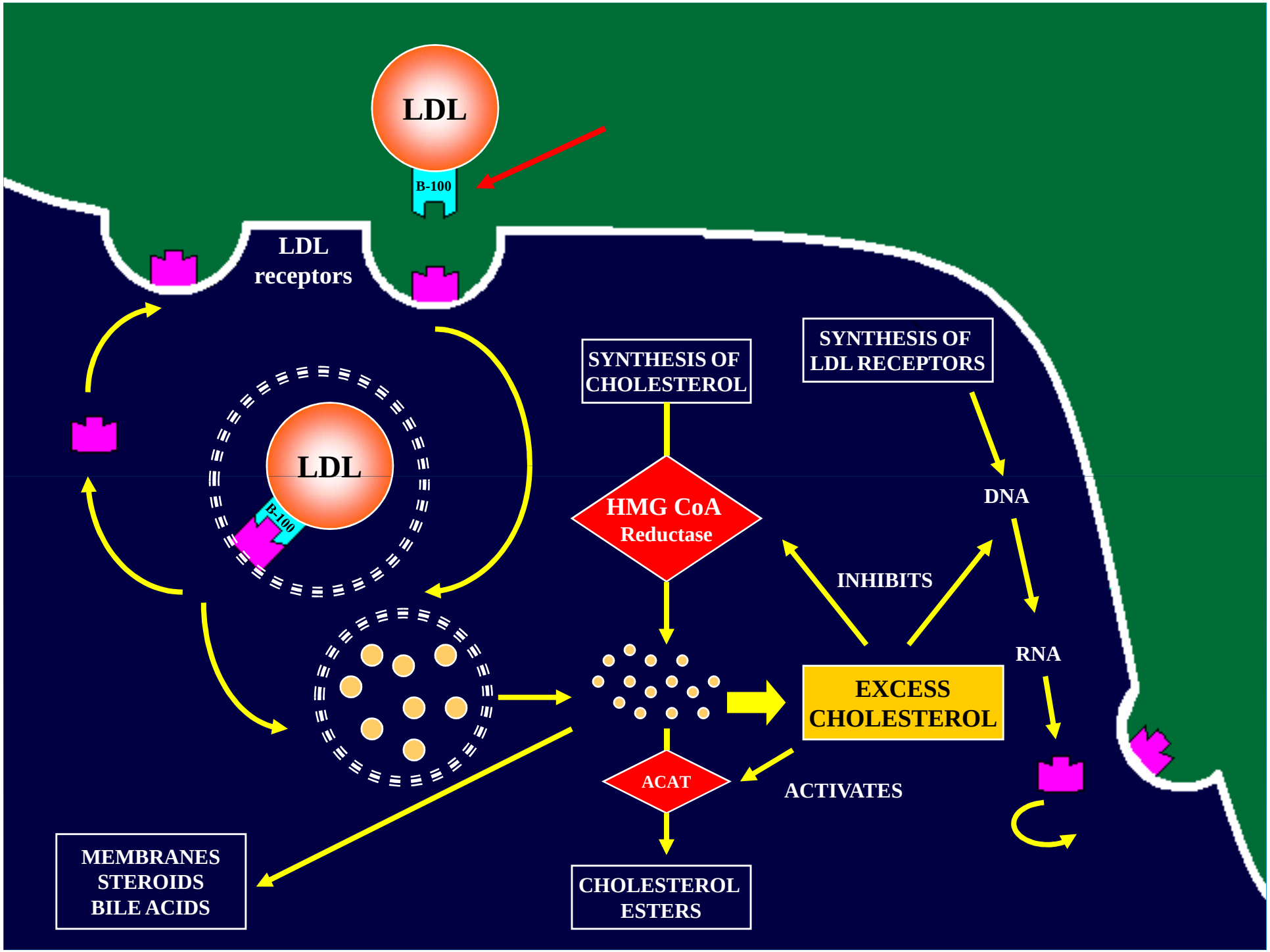
FH-3 (ADH) Heterozygous Homozygous	PCSK9	 ? ?

Apolipoprotein B gene (chr. 2p24)

CGG→TGG Arg3480>Trp
CGG→CAG Arg3500>Gln
CGG→TGG Arg3500>Trp
CGC→TGC Arg3531>Cys
CAC→TAC Arg3543>Tyr

ApoB-100: 4536 aa.


LDL
B-100
LDL receptors
LDL
B-100
SYNTHESIS OF CHOLESTEROL
SYNTHESIS OF LDL RECEPTORS
HMG CoA Reductase
DNA
INHIBITS
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EXCESS CHOLESTEROL
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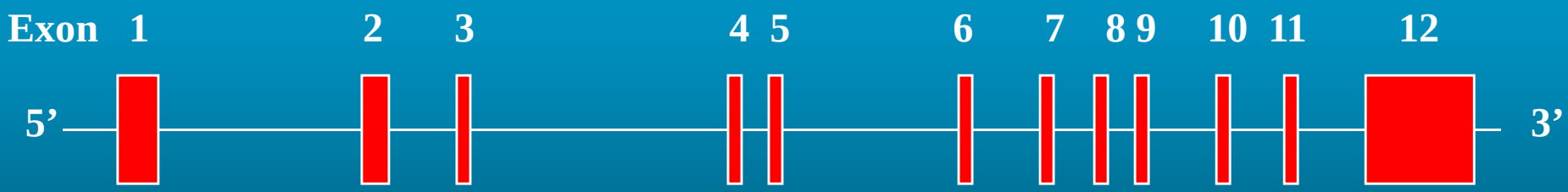
PCSK9 gene (1p32)



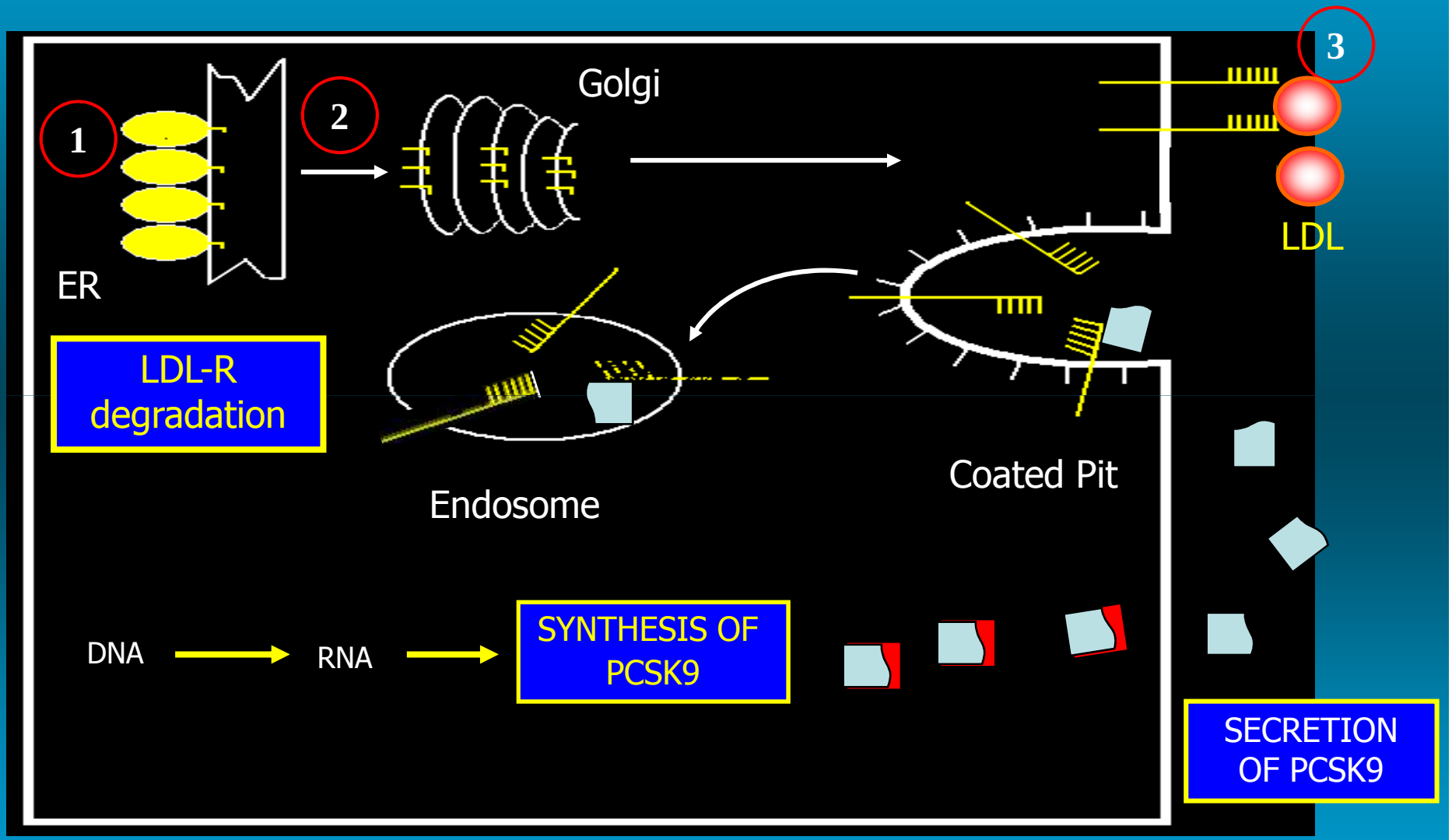
mRNA (3636 nt)

PCSK9 protein (692 aa)

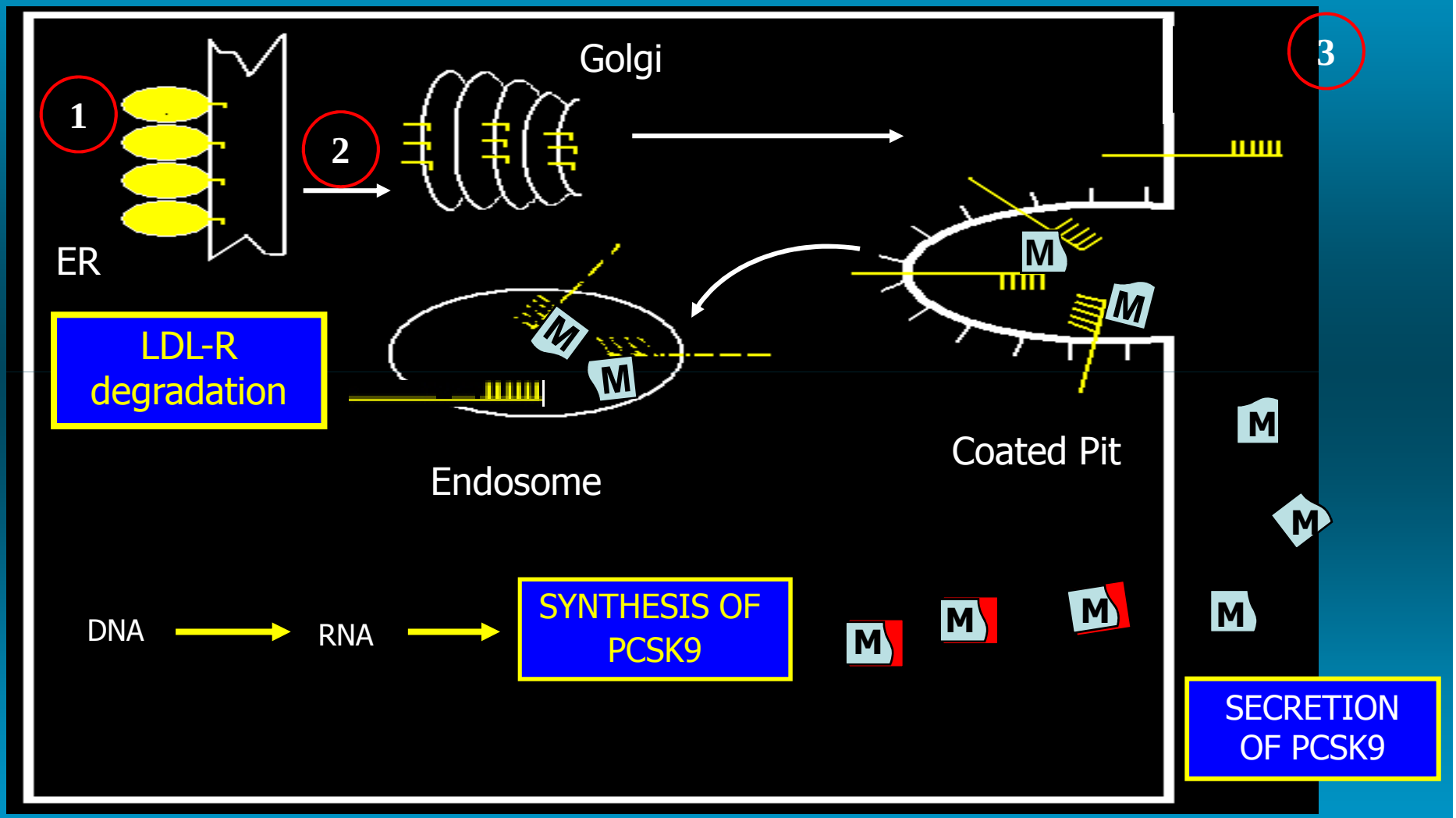
Proprotein Convertase Subtilisin/hexin type 9 Serine Protease

Synthesized by the liver and secreted into the circulation

Regulation of LDL-R number by PCSK9 activity



Reduction of LDL-R number induced by increased PCSK9 activity



INHERITED MONOGENIC HYPERCHOLESTEROLEMIAS

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- Gene dosage effect

Recessive transmission

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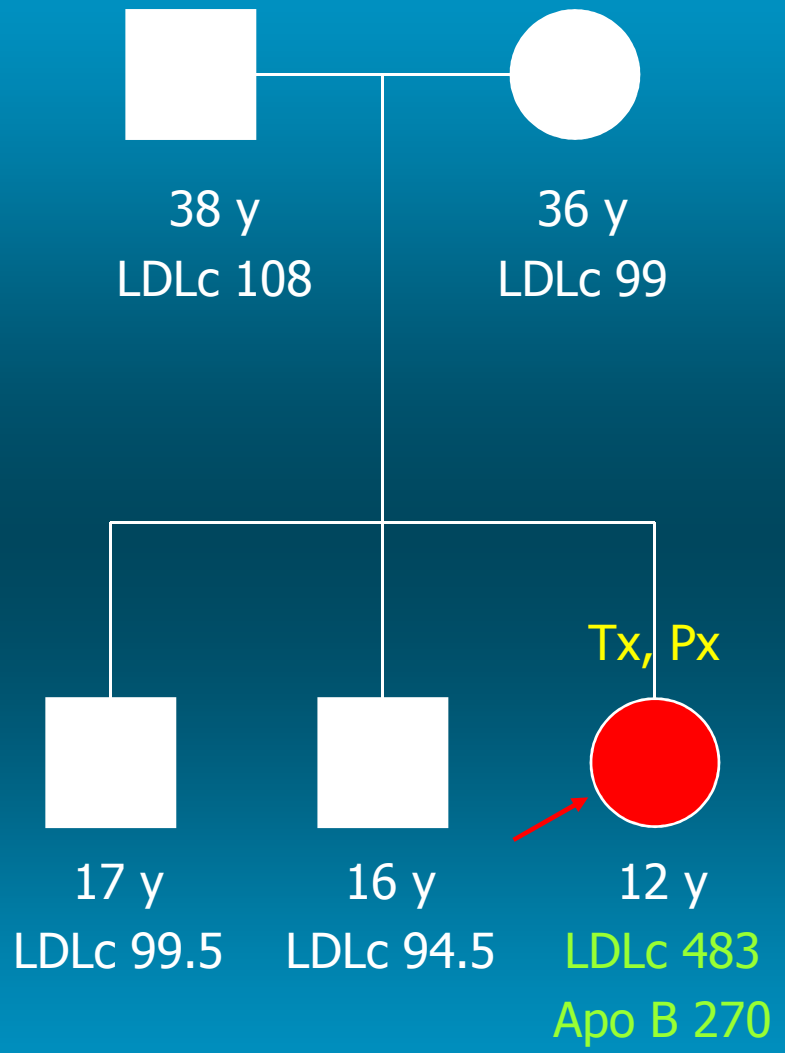
- Homozygote LDL-C ↑ ↑ ↑
  (Two mutant alleles)

M. Family (from Sardinia)



LDL-R activity in fibroblasts

Normal

Affinity of LDL for LDL-R

Normal

FCR of LDL in vivo

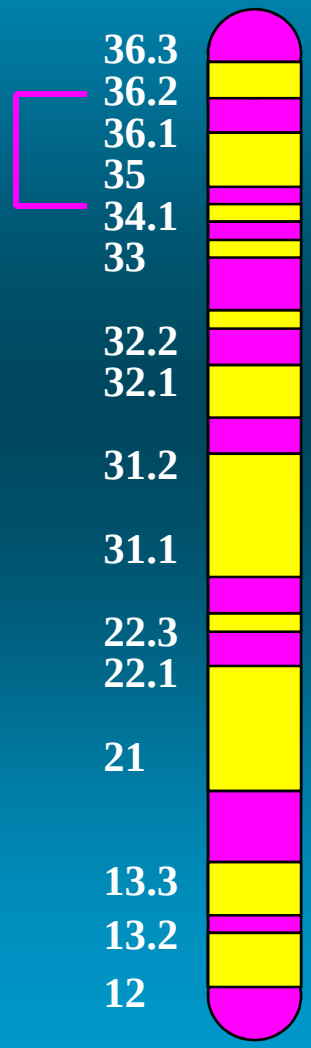
Reduced as in homozygous FH

Clinical diagnosis: Pseudo-homozygous FH

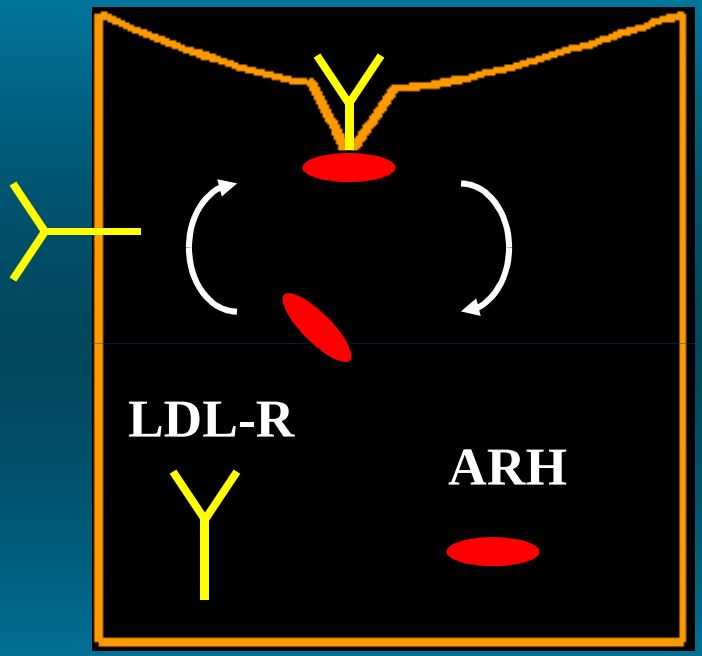
LDLc = mg/dl

Chromosome 1p

ARH 1p36-35



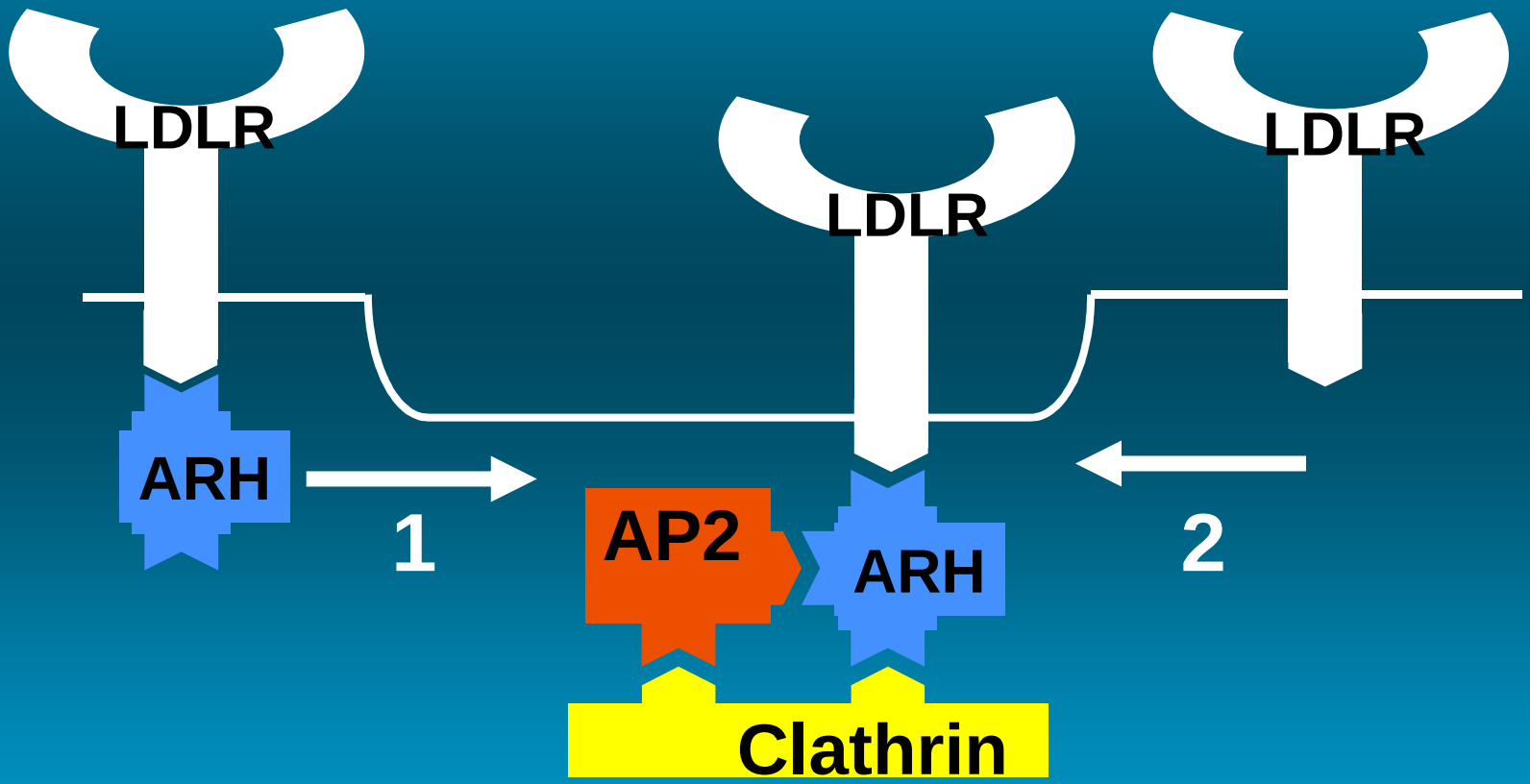
blood



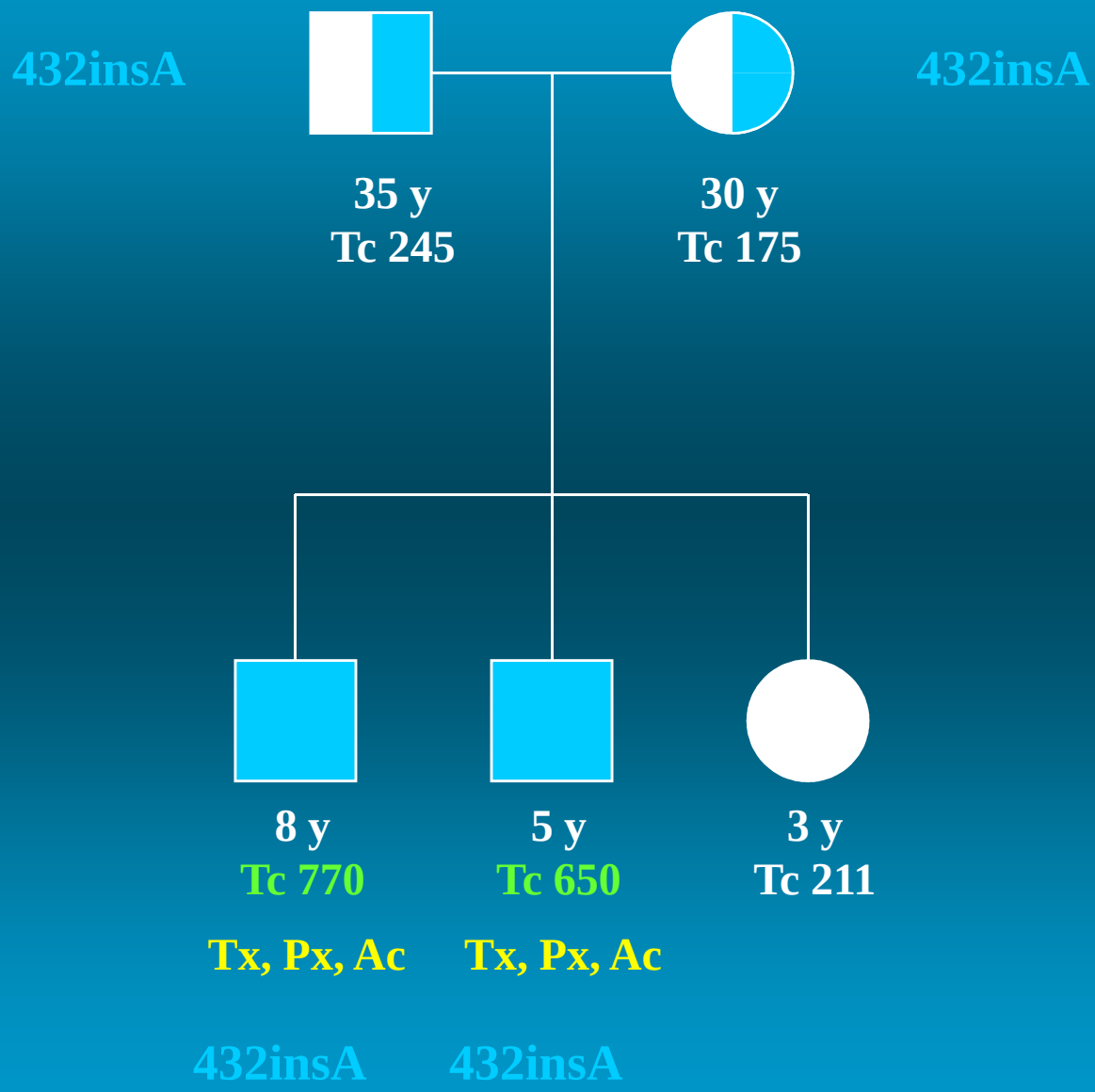
hepatocite

bile

Hypothesis: ARH Clusters LDLR in Coated Pits



S. Family


432insA
432insA
35 y
Tc 245
30 y
Tc 175
8 y
Tc 770
5 y
Tc 650
3 y
Tc 211
Tx, Px, Ac
Tx, Px, Ac
432insA
432insA

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DISLIPIDEMIE

DEFINIZIONE FENOTIPO

↓

INDIVIDUAZIONE NATURA

PRIMITIVA — **SECONDARIA**

↓

DEFINIZIONE GENOTIPO

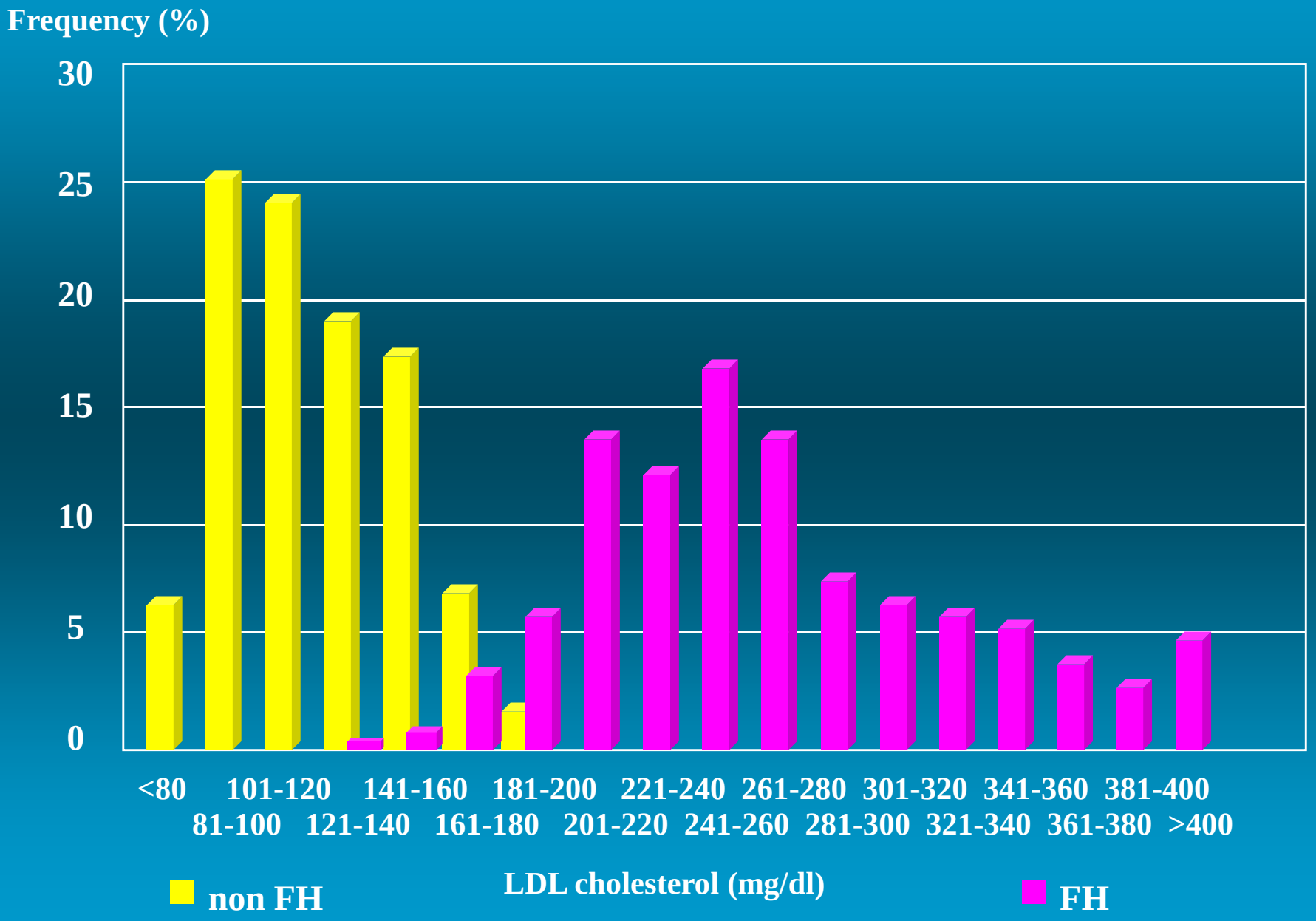
SPORADICA AMBIENTALE

TRASMISSIONE nella FAMIGLIA:
- Co-dominante
- Recessiva

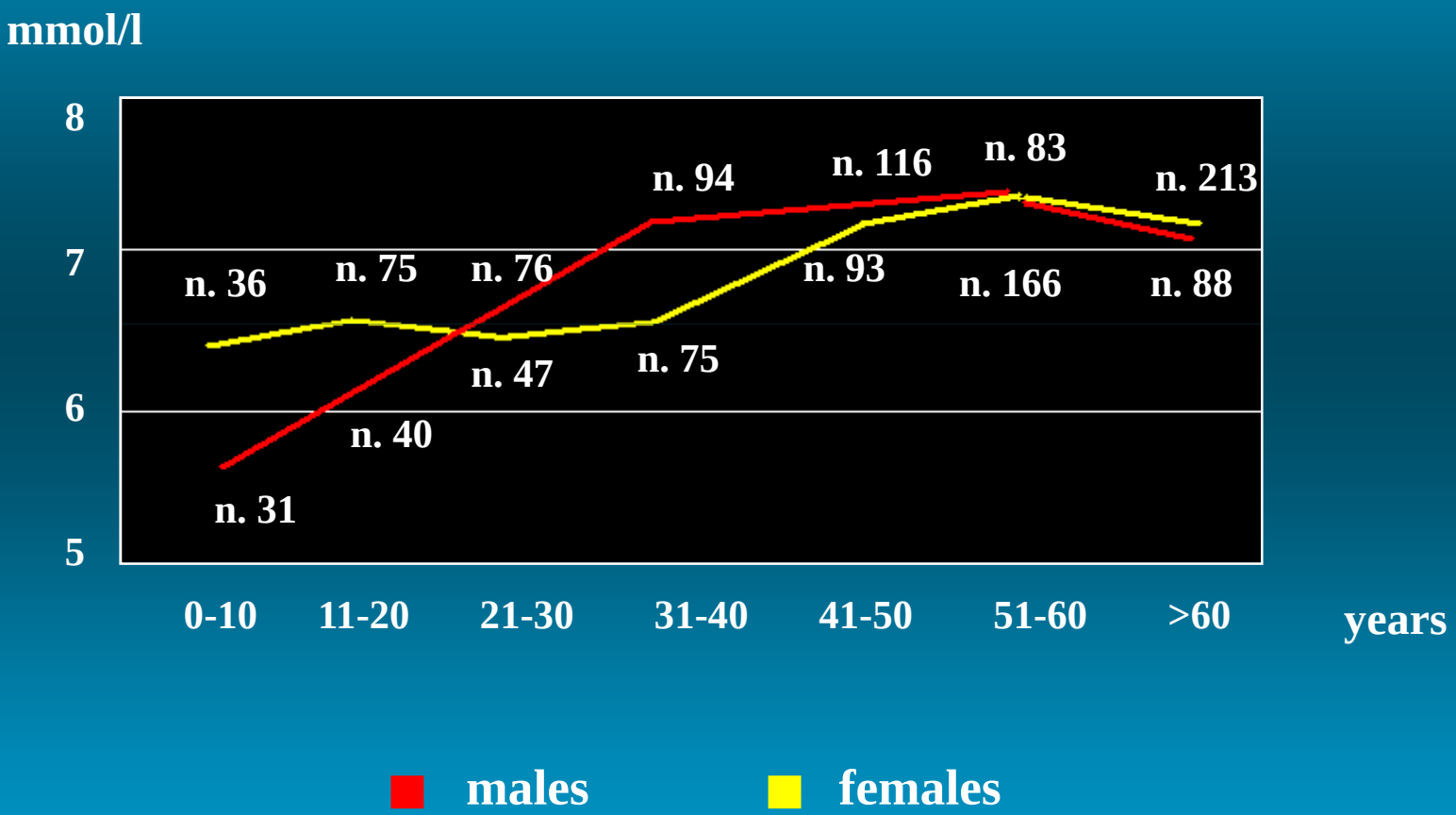
CLINICAL DIAGNOSIS OF FAMILIAL HYPERCHOLESTEROLEMIA

- Plasma LDL-C level
- Clinical history
- Family history
- Clinical score

LDL cholesterol distribution in FH families



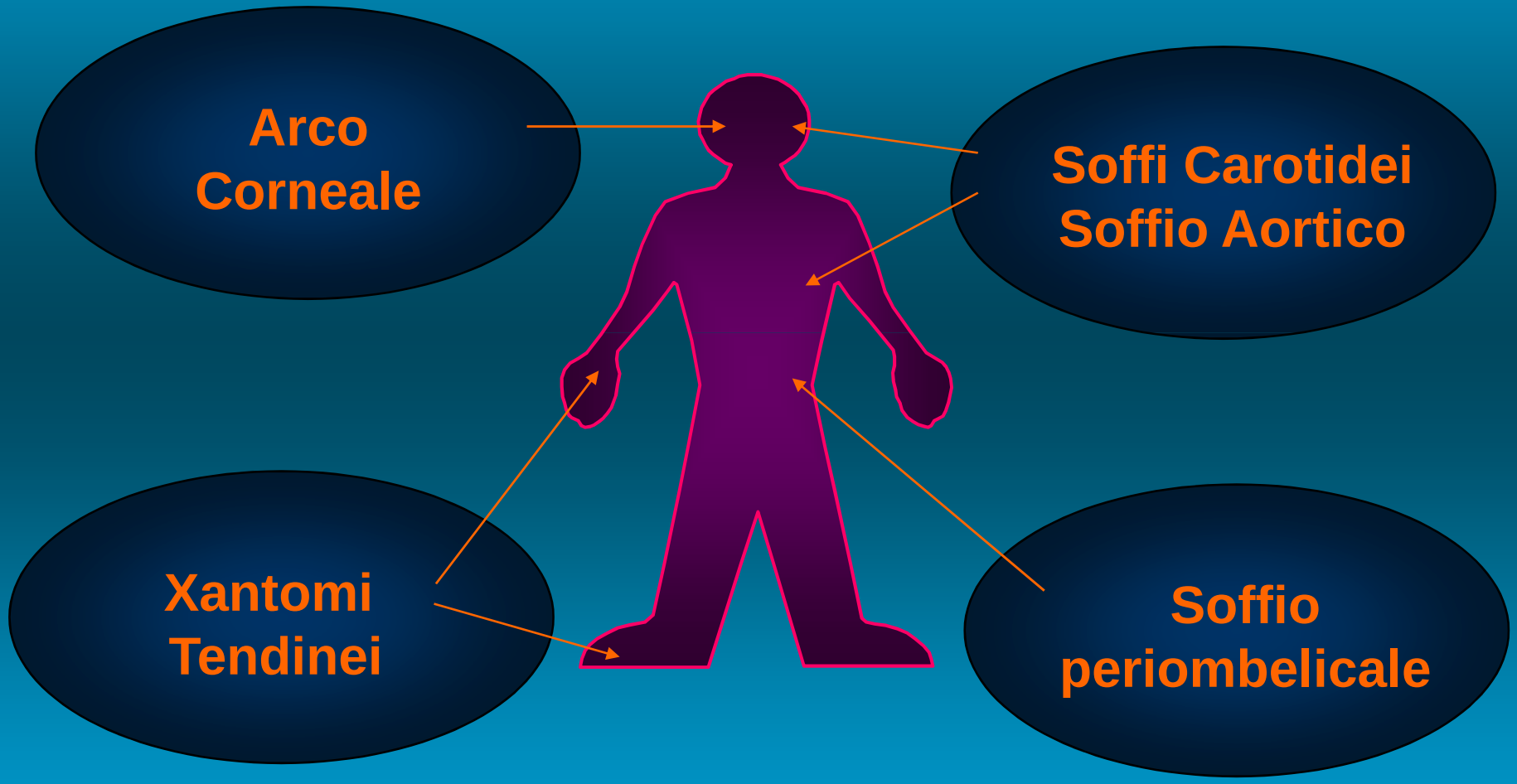
LDL cholesterol levels in FH patients according to age



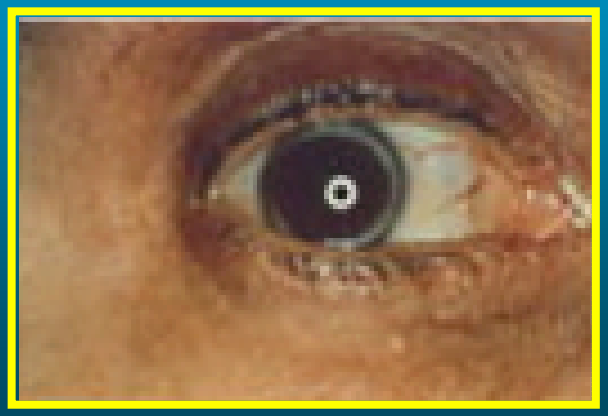
CLINICAL DIAGNOSIS OF FH
Plasma LDL-C level

• LDL-C	> 8.5 *	> 330 **	=	8 p.
• LDL-C	6.5-8.4	250 -329	=	5 p.
• LDL-C	5.0-6.4	190-249	=	3 p.
• LDL-C	4.0-4.9	155-198	=	1 p.
•	* mmol/	** mg/dl		

Approccio clinico al paziente FH 1

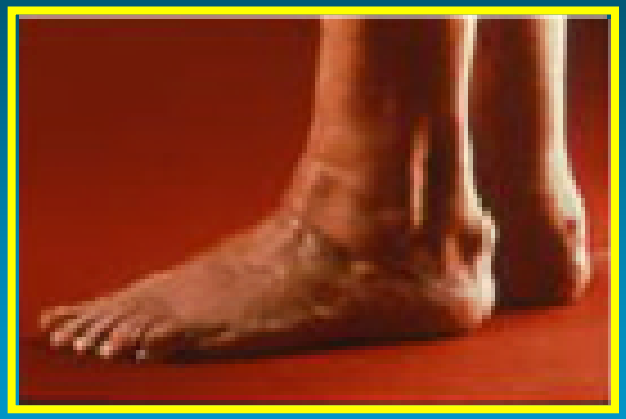


Gerontoxon

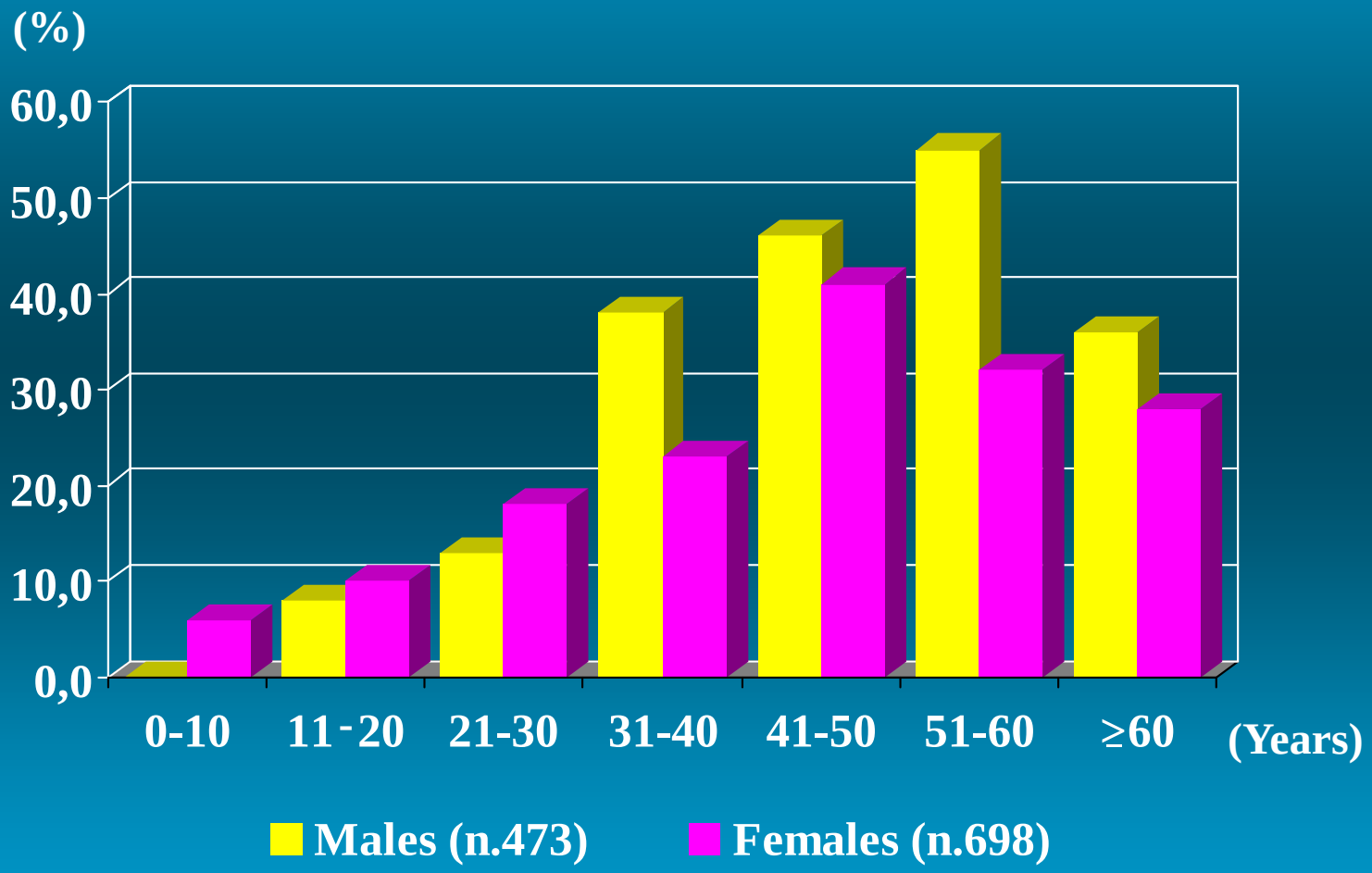


Xanthelasmas

Tendon xanthomas

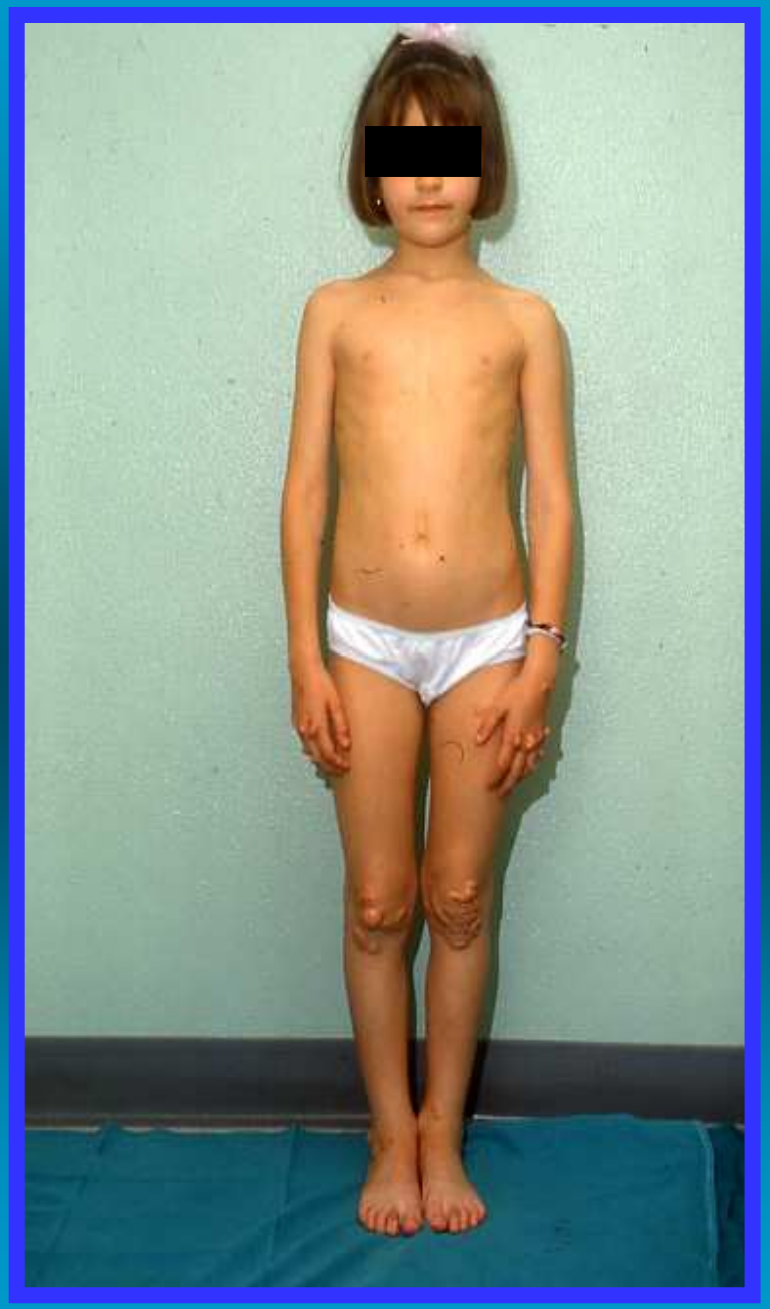


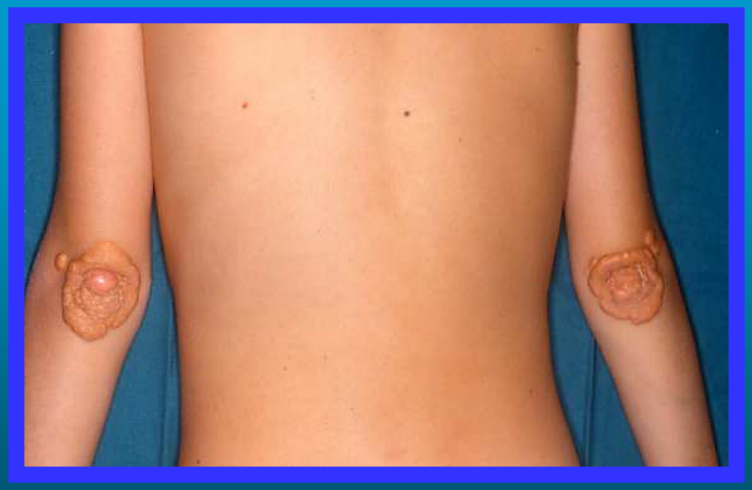
Prevelence of Tendon Xanthomas in FH heterozygous patients

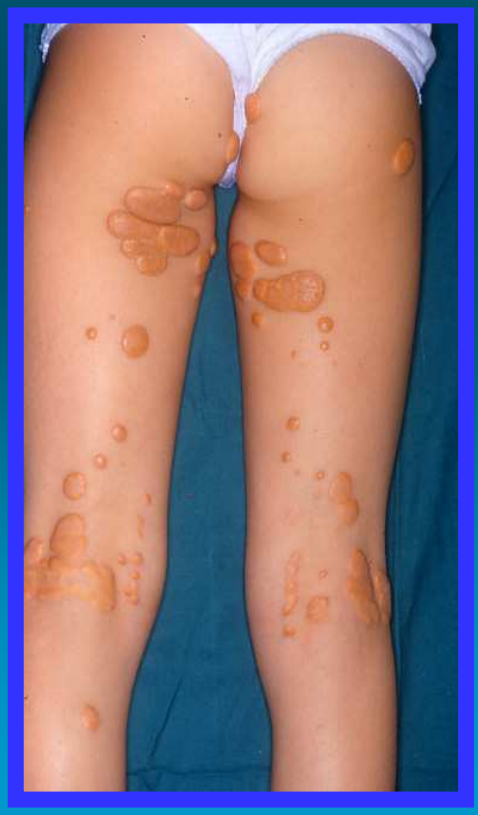


Coefficienti di correlazione r tra aree TC dei tendini e parametri esaminati

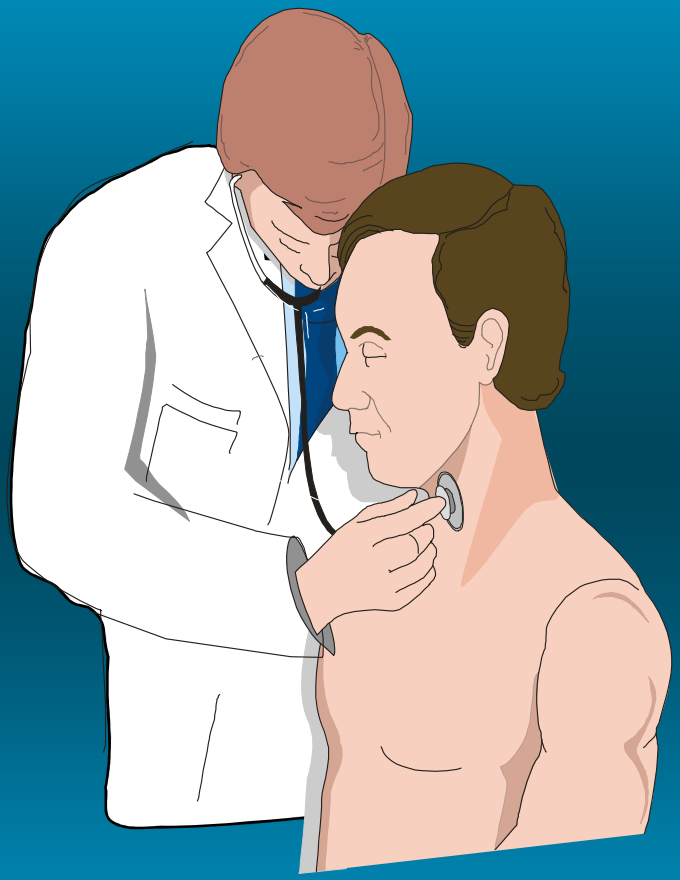
• ETA’	0.22	p< 0.05
• BMI	0.20	0.067
• CT	0.47	p< 0.001
• LDL-C	0.53	p< 0.001
• HDL-C	-0.35	p< 0.005
• CT/HDL-C	0.63	p< 0.001
• TG	0.01	0.45

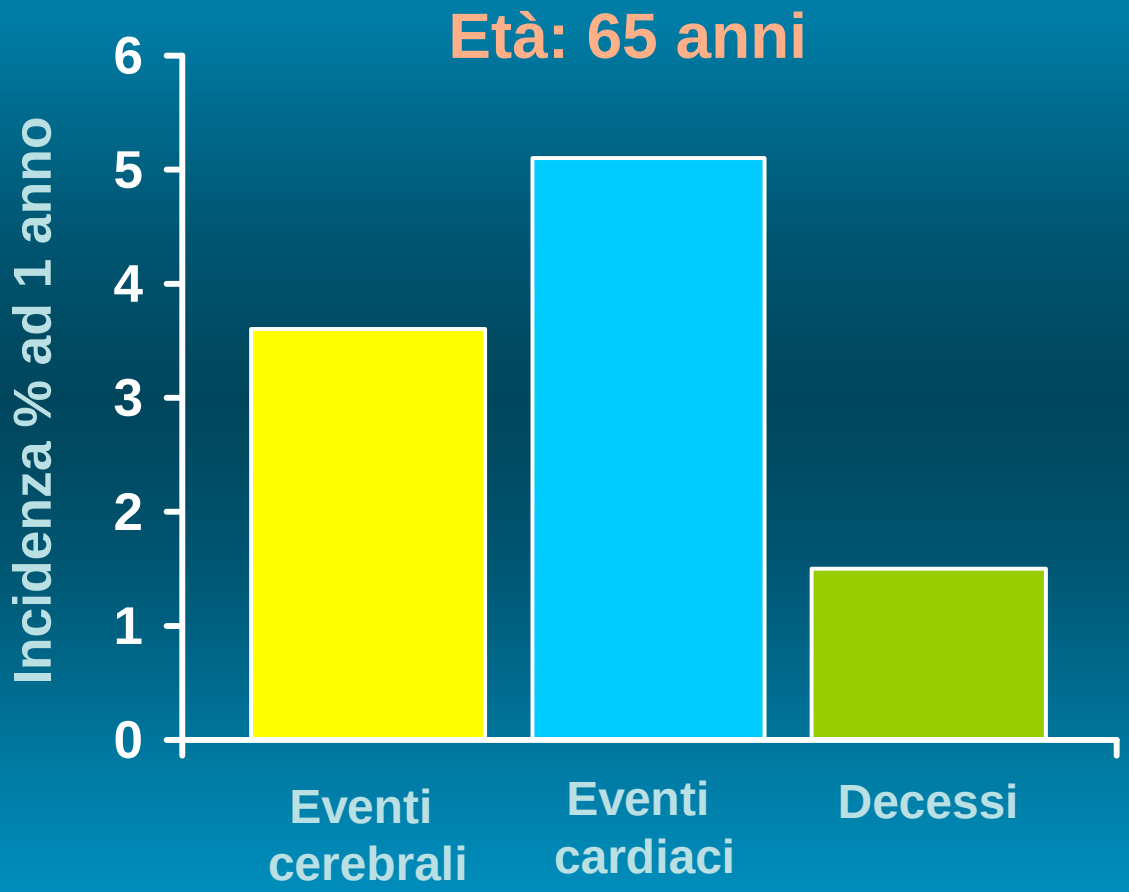




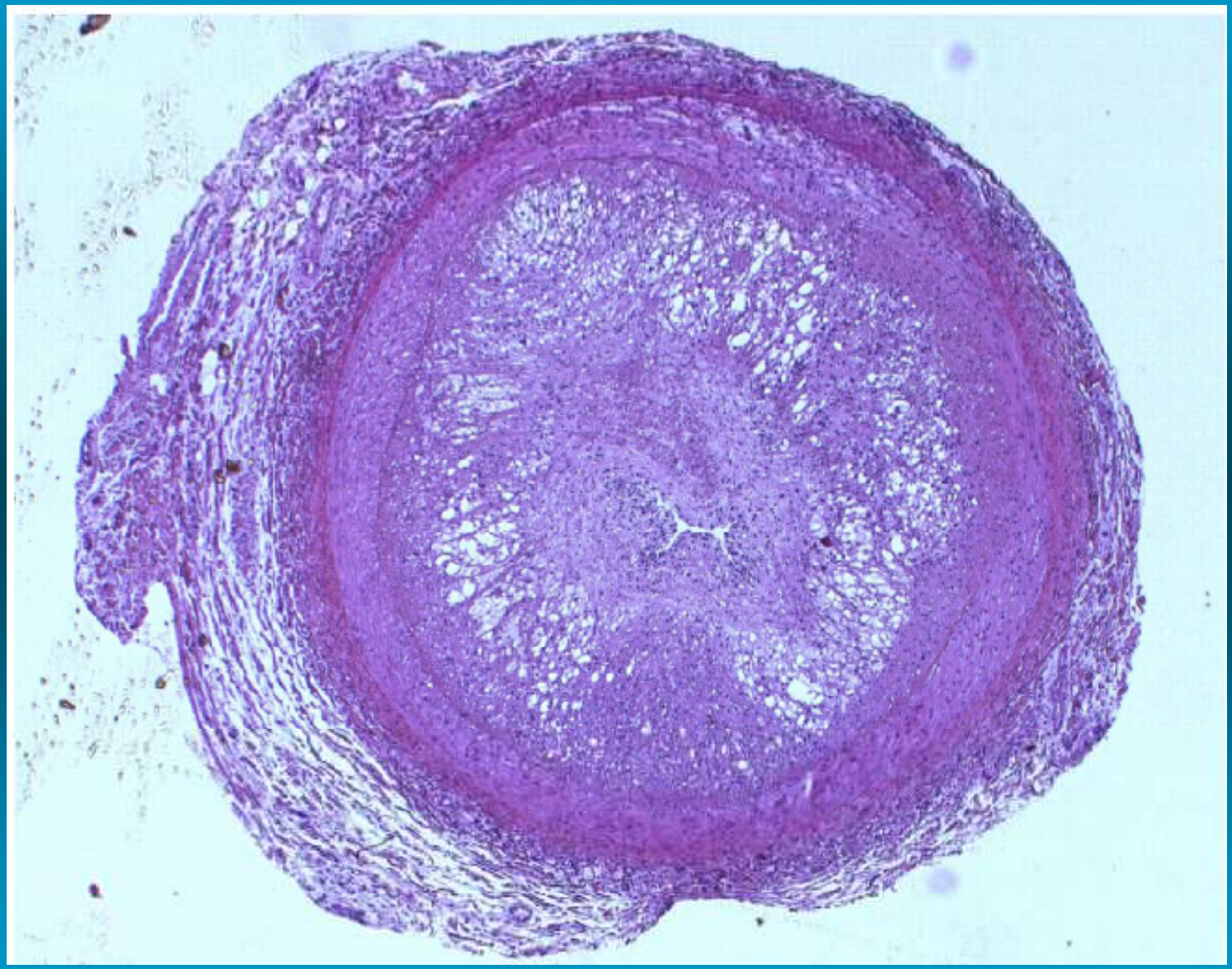


Soffi carotidei

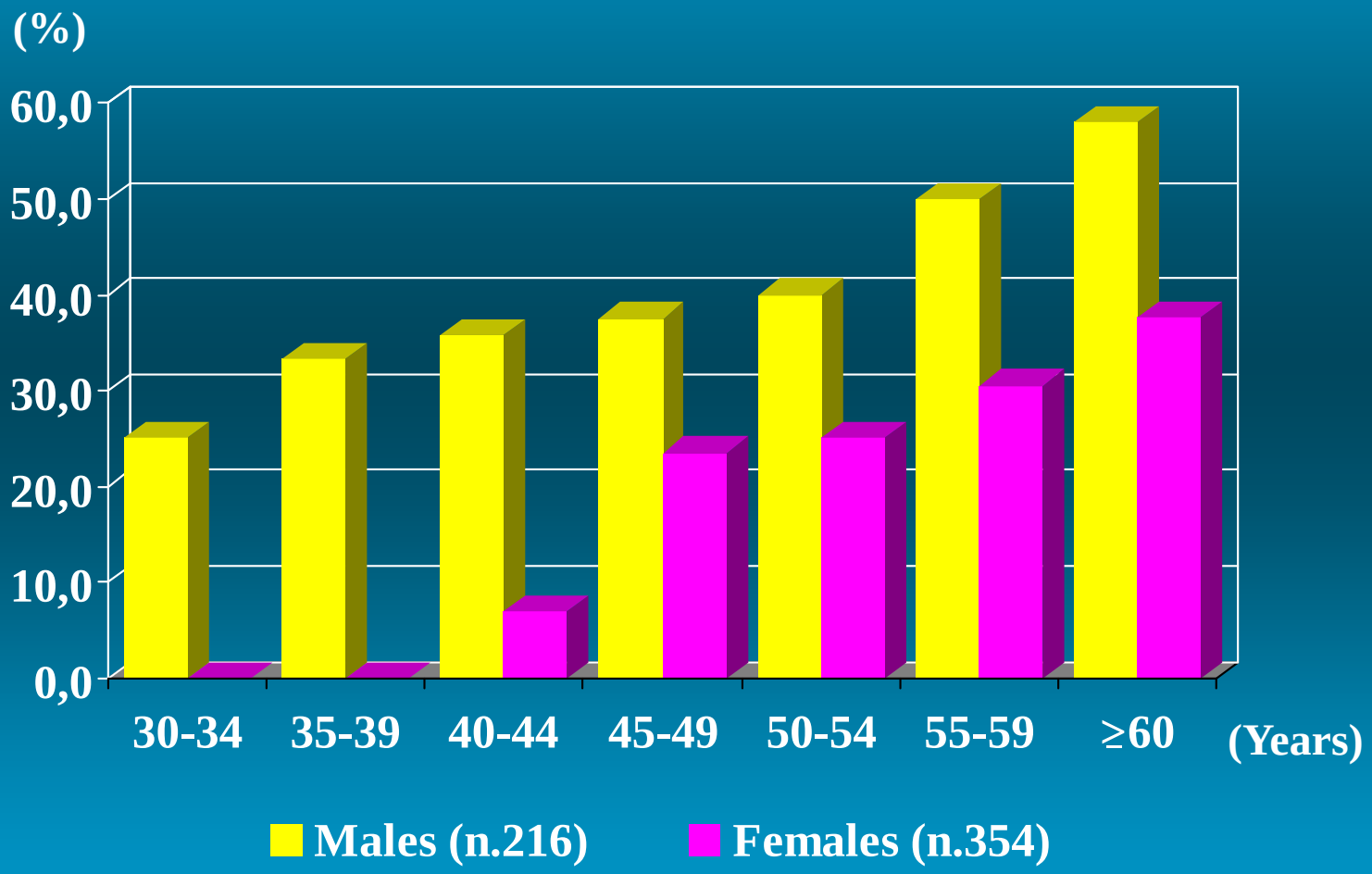




Chambers BR et al. N Engl J Med 1986;315:860-865



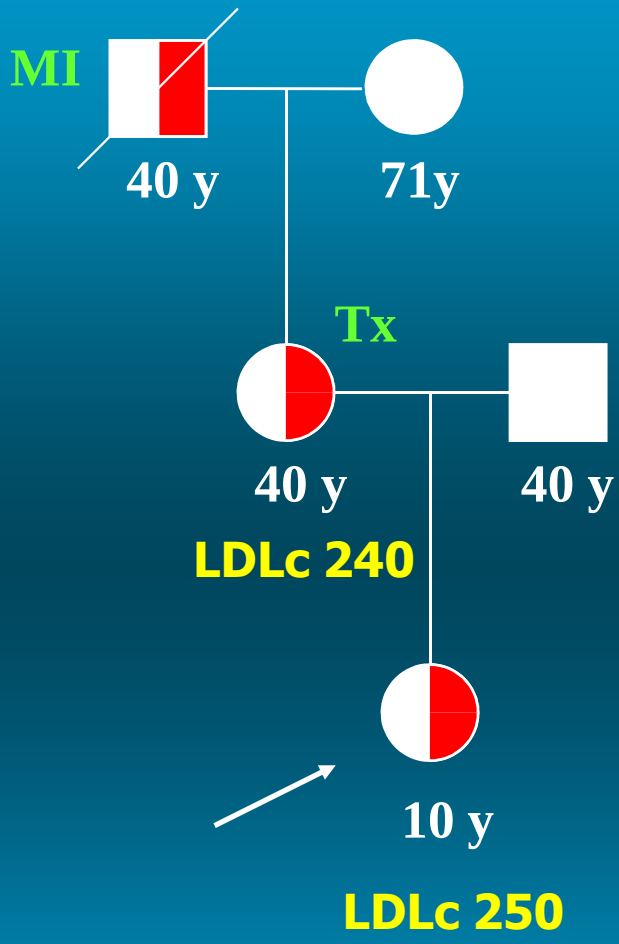
CHD in Italian FH heterozygotes



CLINICAL DIAGNOSIS OF FH
Clinical History

- Patient with pCAD = 2 p.
- Patient with premature cerebral/peripheral artery disease = 1 p.
- Tendon Xanthomas = 6 p.
- Arcus Cornealis = 4 p.

CLINICAL DIAGNOSIS OF DEFINITE FH



Lipids mg/dl

Tx = tendon xanthomas MI = myocardial infarction

CLINICAL DIAGNOSIS OF FH
Family History

- First degree relative with pCAD = 1 p.
- First degree relative with LDL-C > 95° = 1 p.
- First degree relative with Tx = 2 p.
- Children <18 with LDL-C >95° = 2 p.

CLINICAL DIAGNOSIS OF FH
Final Score

- Definite FH score > 8 p.
- Probable FH score 6 – 8 p.
- Possible FH score 3 – 5 p.
- No diagnosis score < 3 p.

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DISLIPIDEMIA FAMILIARE COMBINATA FCHL

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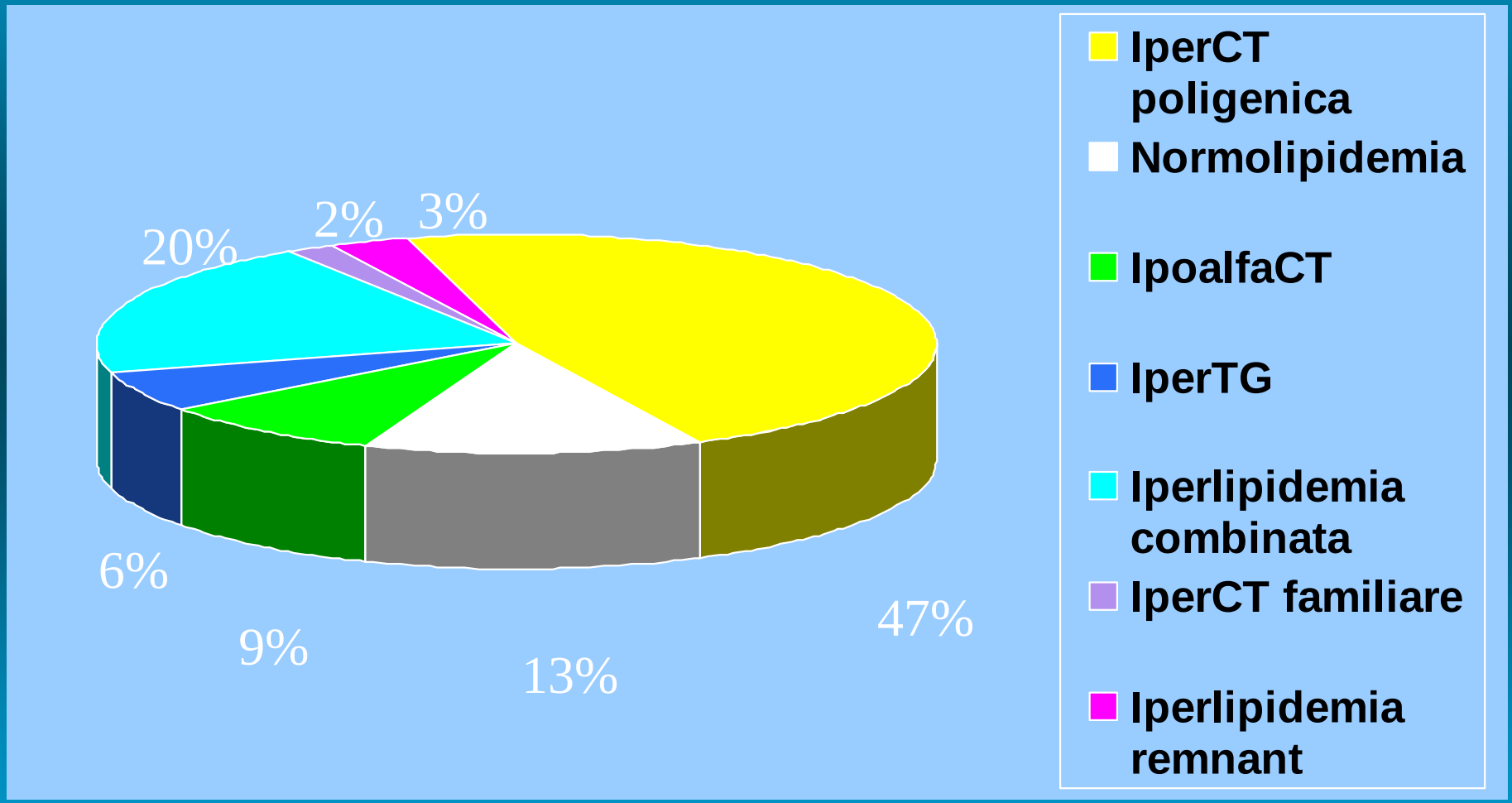
Hyperlipidemia in Coronary Heart Disease

II. GENETIC ANALYSIS OF LIPID LEVELS IN 176 FAMILIES AND DELINEATION OF A NEW INHERITED DISORDER, COMBINED HYPERLIPIDEMIA

JOSEPH L. GOLDSTEIN, HELMUT G. SCHROTT, WILLIAM R. HAZZARD, EDWIN L. BIERMAN, and ARNO G. MOTULSKY with the technical assistance of ELLEN D. CAMPBELL and MARY JO LEVINSKI

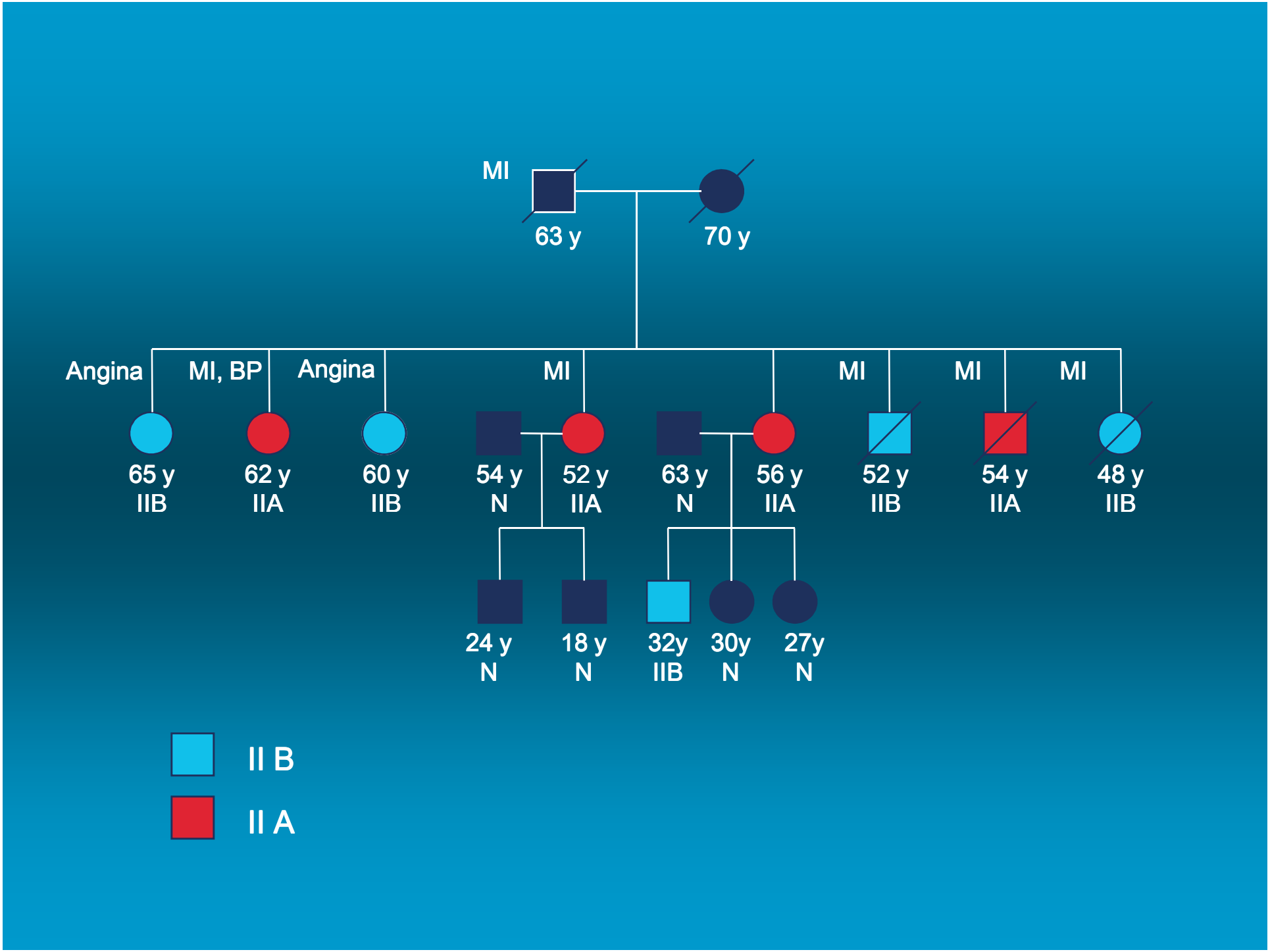
The Journal of Clinical Investigation Volume 52 July 1973 · 1544–1568

DISLIPIDEMIA nei sopravissuti a IMA (n=807)

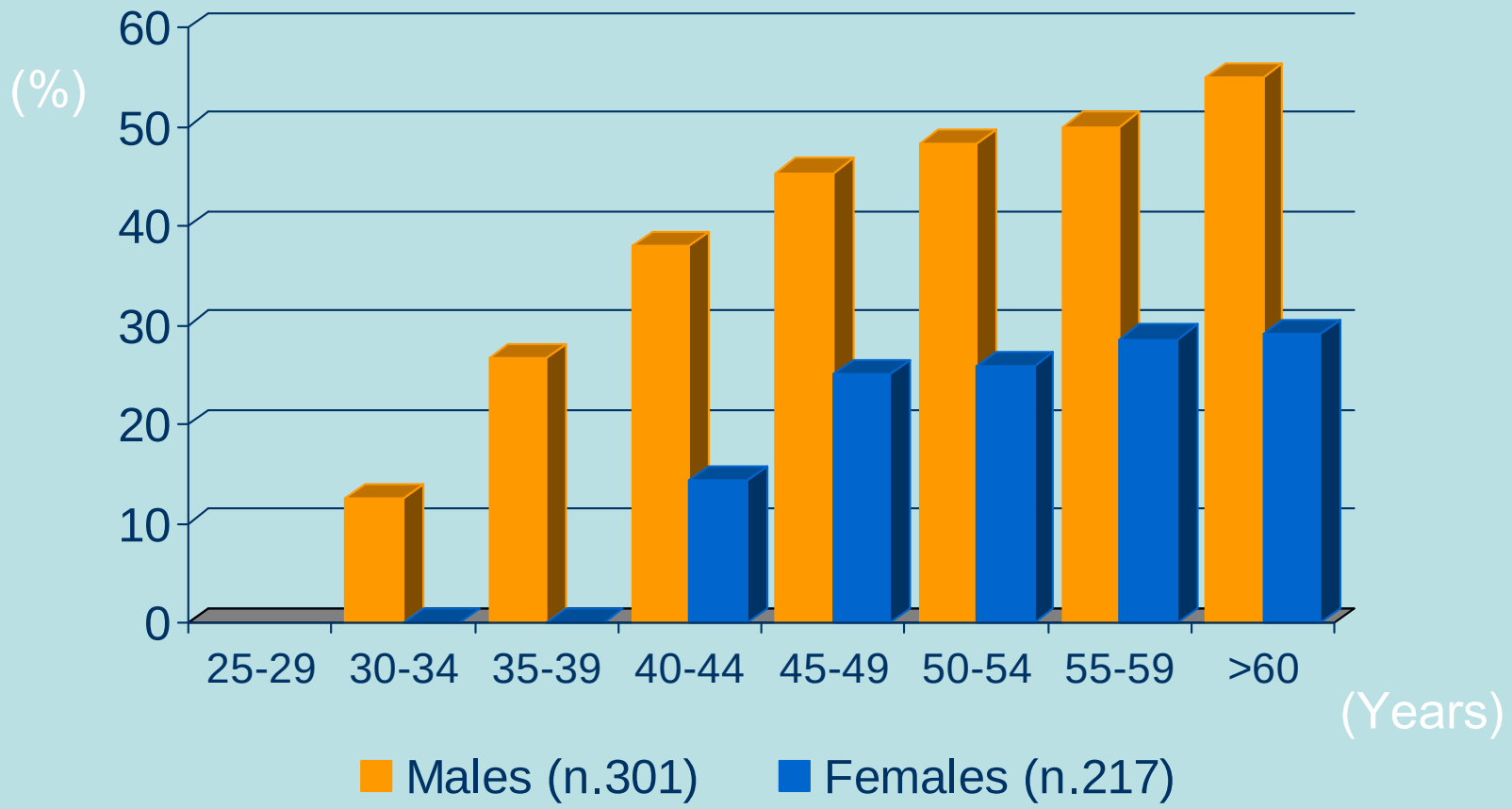


FAMILIAL COMBINED HYPERLIPIDAEMIA (FCHL)

- Common (1-3:100)
- Cholesterol and/or triglyceride levels are elevated, usually to only a moderate extent, reflecting increased LDL and/or VLDL
- FAMILIAL: 1st degree relatives with different phenotypes
- HDL may be low
- Characterized by overproduction of apoB-100
- Coronary heart disease risk increased


MI
63 y
70 y
Angina
MI, BP
Angina
MI
MI
MI
MI
65 y
IIB
62 y
IIA
60 y
IIB
54 y
N
52 y
IIA
63 y
N
56 y
IIA
52 y
IIB
54 y
IIA
48 y
IIB
24 y
N
18 y
N
32y
IIB
30y
N
27y
N
II B
II A

CHD in Italian FCHL



FCHL nei bambini

- **La FCHL rappresenta la più frequente (47%) dislipidemia genetica in bambini che afferiscono ad una “lipid clinic” pediatrica.**
- **La manifestazione fenotipica più frequente è rappresentata da un aumento combinato di CT e TG**
- **I livelli dei lipidi plasmatici nei bambini con FCHL sono molto “sensibili” al peso corporeo, all’insulinemia (i.e. TG) e all’età (i.e. CT).**
- **Queste osservazioni suggeriscono che il controllo del peso corporeo può essere un utile approccio terapeutico alla FCHL in età pediatrica.**

Caratteristiche dei bambini

	Famiglie FCHL		Famiglie Normali
	Affetti (n = 98)	Non affetti (n = 9)	(n = 28)
Età	9.0 ± 4.3	9.9 ± 4.6	8.2 ± 4.3
BMI (kg/m^2)	19.0 ± 3.7	19.7 ± 2.7	18.3 ± 3.2
Lipidi (mg/dl)			
Colesterolo	216.4 ± 39.7***	158.7 ± 6.6†	148.1 ± 14.7
HDL-C	51.3 ± 14.3	44.0 ± 7.5†	52.0 ± 9.7
Trigliceridi	131.7 ± 74.2***	63.3 ± 16.0	59.9 ± 17.1
LDL-C	138.6 ± 42.6**	102.0 ± 11.9††	84.1 ± 16.5
Apo B	97.6 ± 30.0**	71.8 ± 8.4 †	59.2 ± 11.6
Glicemia	82.5 ± 12.0	83.5 ± 21.7 ††	64.9 ± 9.2
Insulina (µU/ml)	8.7 ± 6.8	8.9 ± 6.4	5.7 ± 4.0

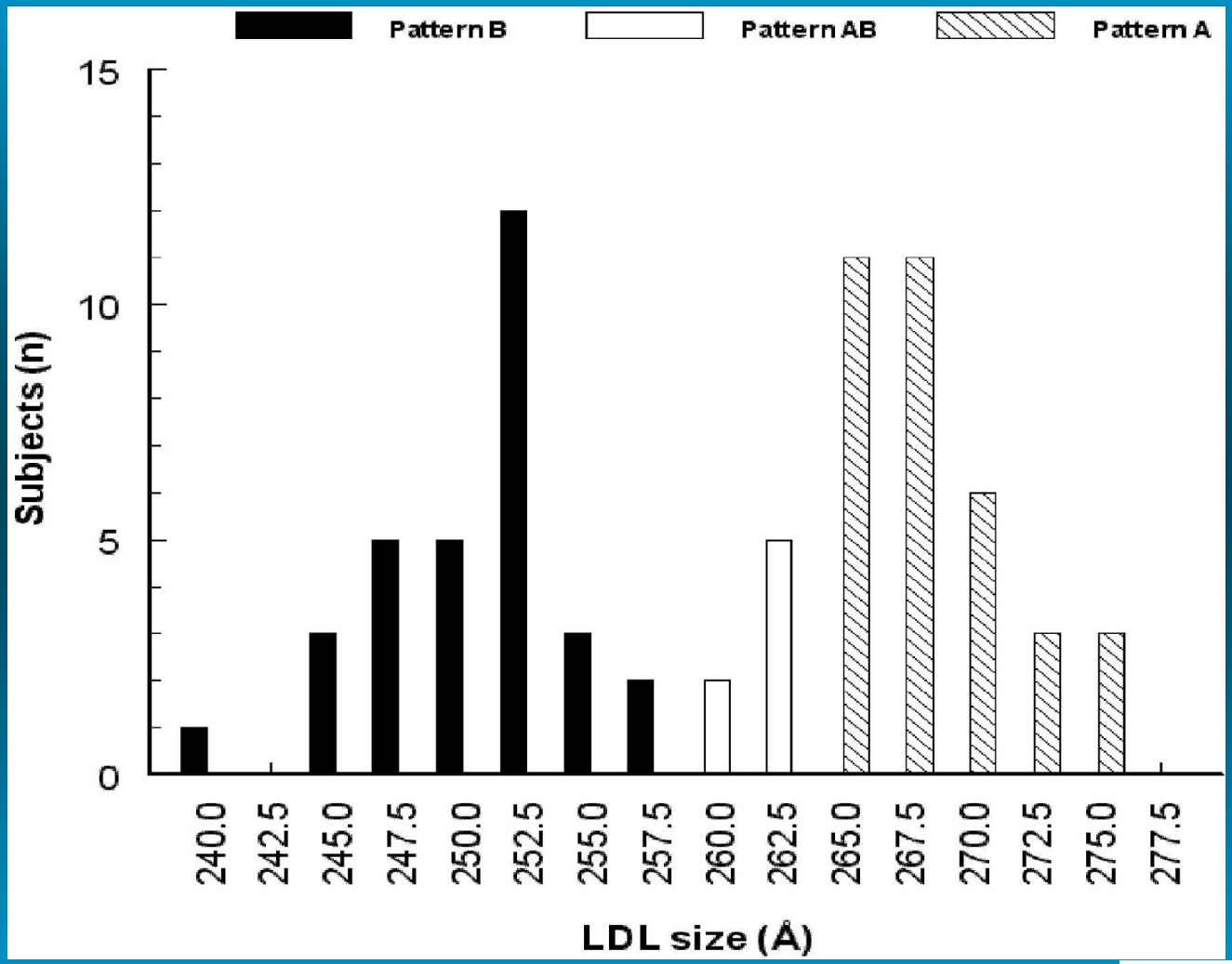
****p<0.001; ***p<0.001 affetti FCHL vs non affetti †p<0.05; ††p<0.01 non affetti FCHL vs Normali**

Caratteristiche dei genitori

	Famiglie FCHL		Famiglie Normali
	Affetti (n = 61)	Non affetti (n = 51)	(n = 38)
Età	**40.1 ± 5.9**	**39.3 ± 4.6**	**37.5 ± 6.0**
BMI (kg/m^2)	**26.8 ± 3.7*****	**24.1 ± 3.4**	**24.7 ± 3.9**
Lipidi (mg/dl)			
Colesterolemia	**246.5 ± 58.7*****	**186.3 ± 28.2**	**181.8 ± 21.4**
HDL-C	**47.1 ± 17.0**	**48.7 ± 9.4††**	**55.7 ± 15.6**
Trigliceridemia	**265.9 ± 183.6*****	**91.1 ± 28.7**	**85.8 ± 32.5**
LDL-C	**150.1 ± 65.1****	**119.3 ± 24.8†**	**109.0 ± 24.6**
Apo B	**140.5 ± 50.0****	**91.8 ± 19.1**	**83.8 ± 18.9**
Glicemia	**93.0 ± 31.1***	**81.4 ± 15.4†††**	**69.0 ± 13.1**
Insulinemia (uU/ml)	**10.0 ± 6.1**	**8.6 ± 13.8**	**6.6 ± 4.7**

*p<0.05;**p<0.01;***p<0.001 affetti vs non affetti †p<0.05; ††p<0.01; †††p<0.001 non affetti vs normali

Frequency distribution of LDL size in hyperlipidemic FCHL relatives



Georgieva, A.M. et al. Arterioscler Thromb Vasc Biol 2004;24:744-749

Arteriosclerosis, Thrombosis, and Vascular Biology

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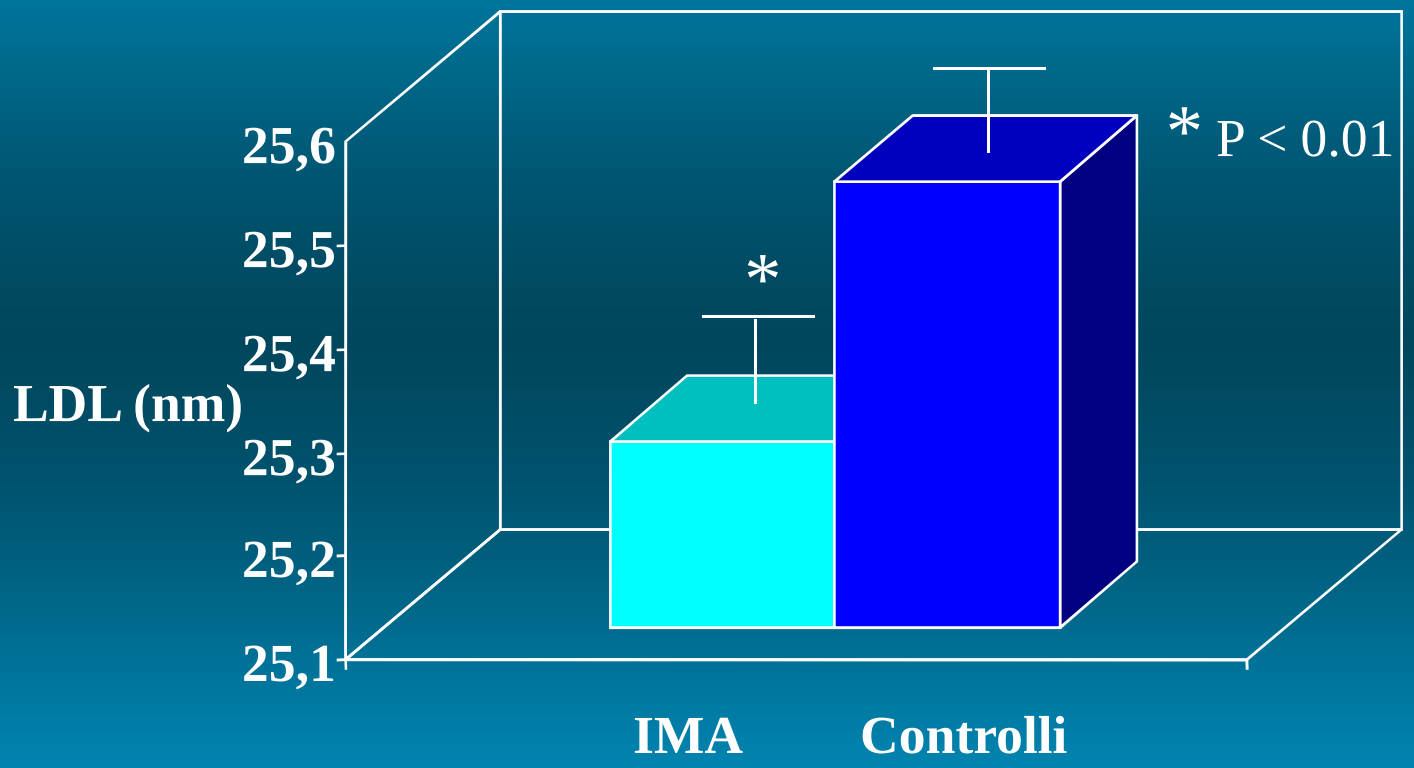
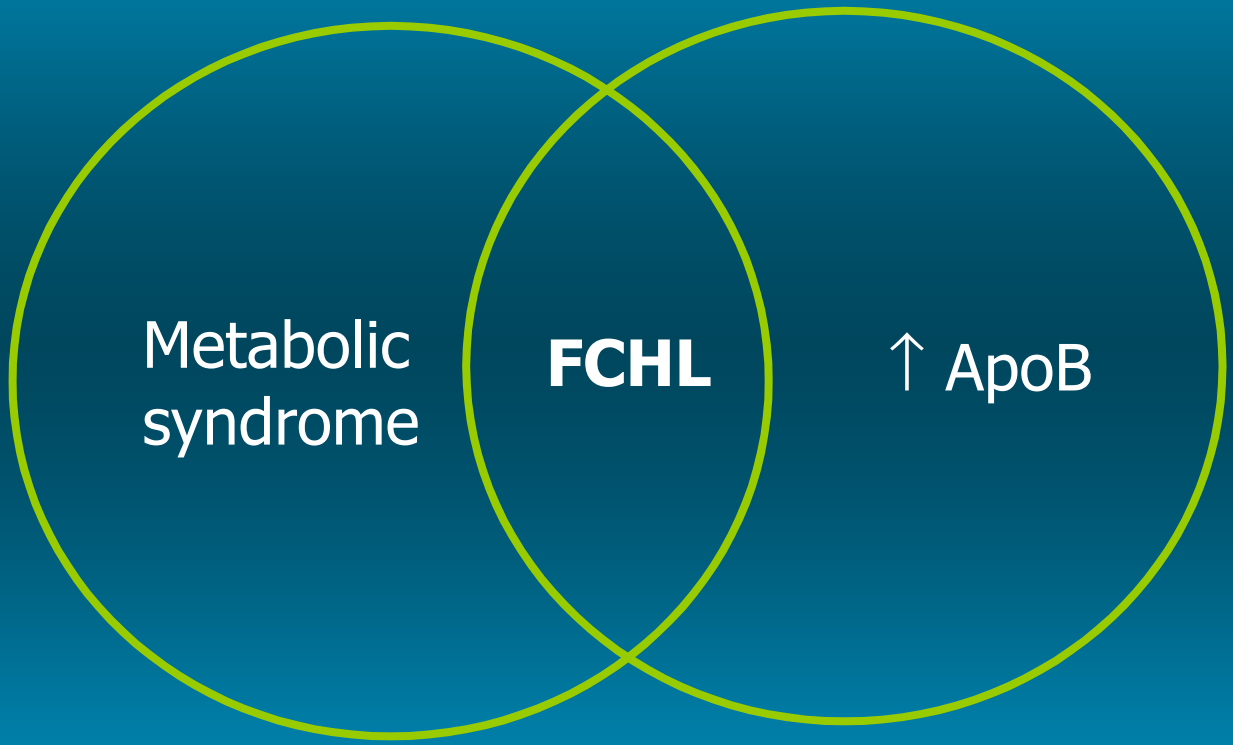
Dimensioni delle LDL negli infartuati e nei controlli



Valori corretti per colesterolemia HDL, trigliceridemia, colesterolemia totale, sesso, diabete, ipertensione arteriosa, familiarità cardiovascolare



Arteriosclerosis, Thrombosis, and Vascular Biology. 2003;23:1289

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SERVIZIO di DIABETOLOGIA &
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AZIENDA OSPEDALIERO-UNIVERSITARIA
OSPEDALE di CATTINARA - TRIESTE

LIPOPROTEINA(a)
Lp(a)

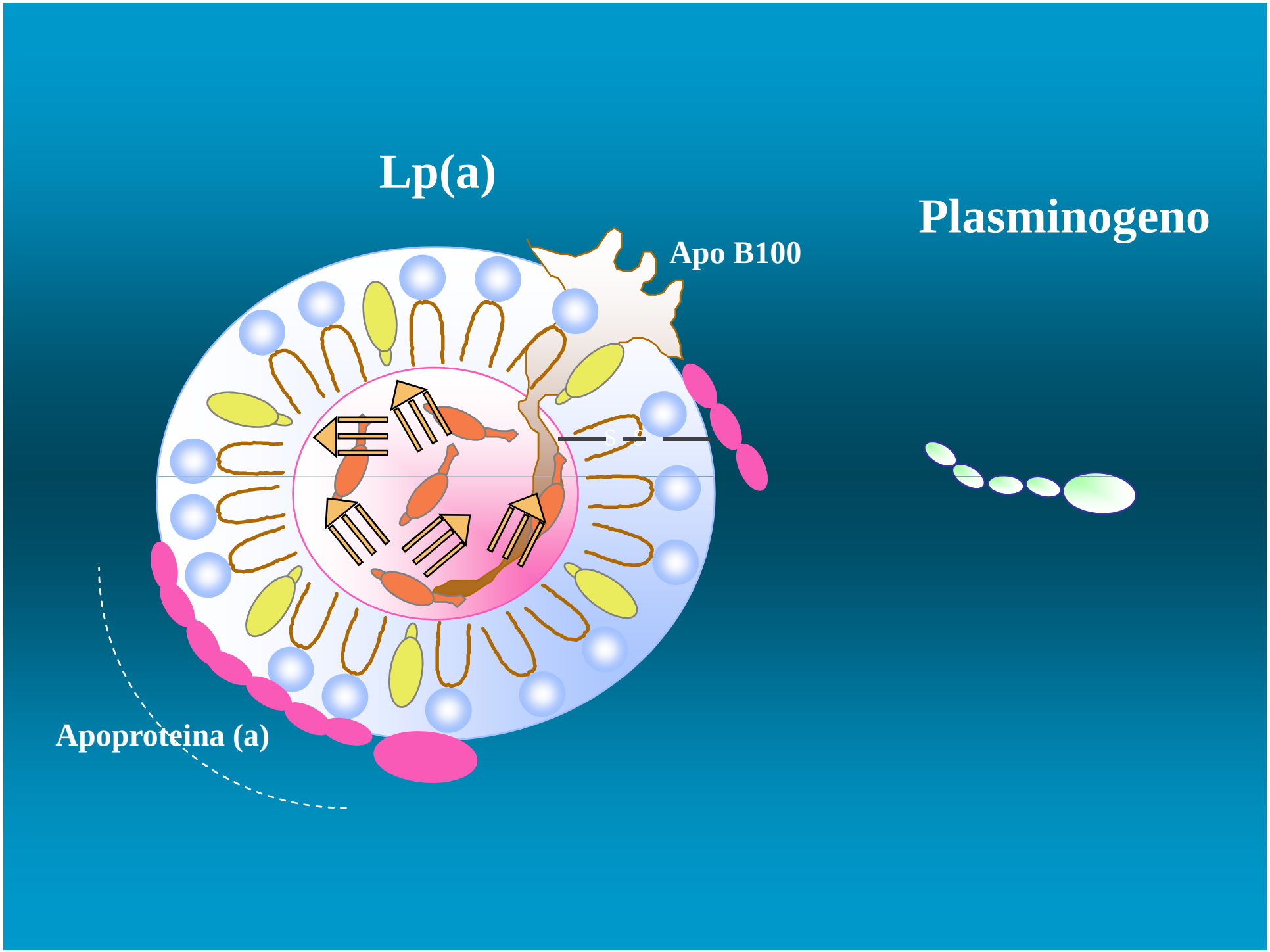
SIdEM
Società Italiana di Emaferesi e Manipolazione Cellulare

XV CONGRESSO NAZIONALE DELLA SOCIETA' ITALIANA DI EMAFERESI E MANIPOLAZIONE CELLULARE

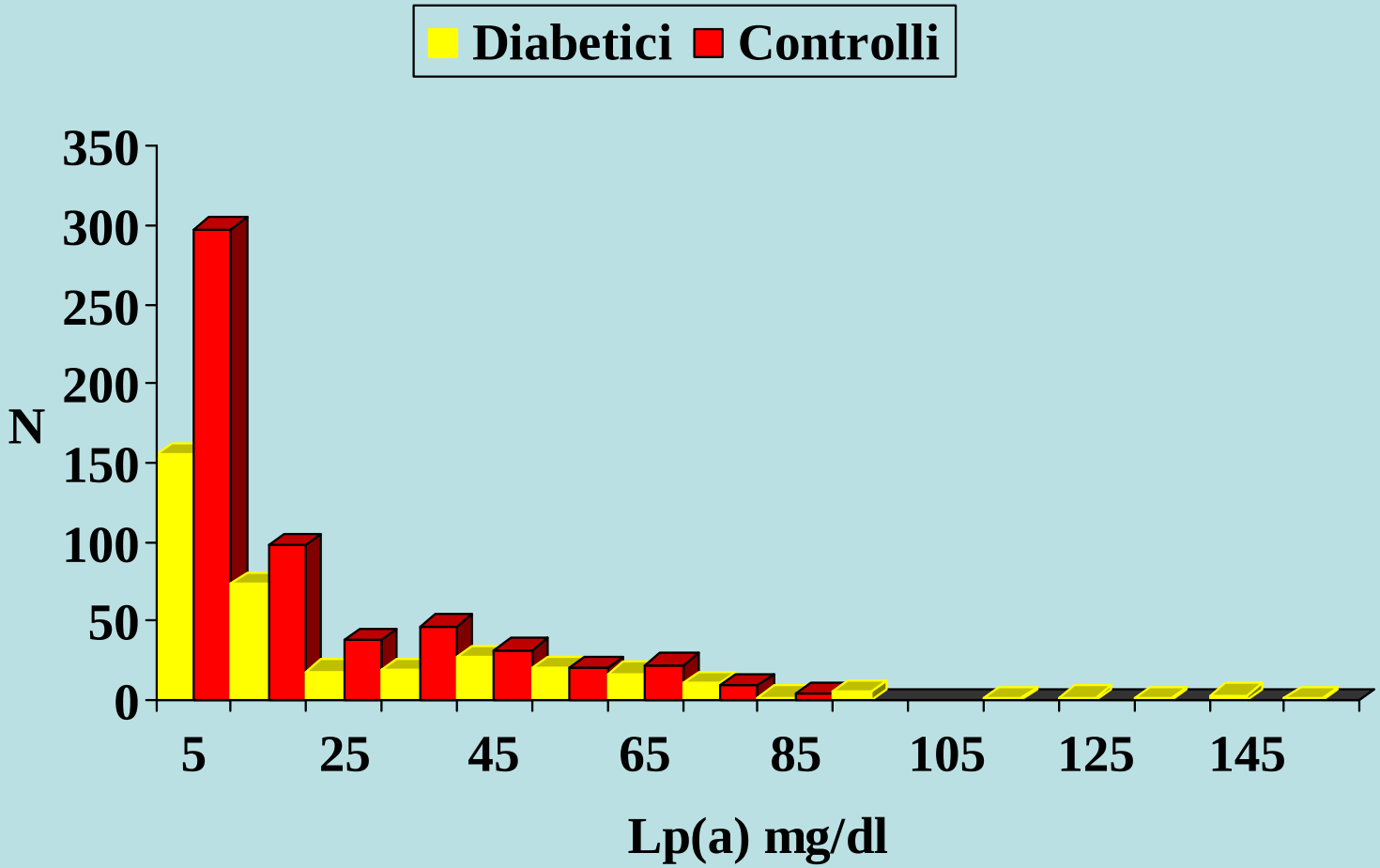
XVI CORSO DI AGGIORNAMENTO IN EMAFERESI PER PERSONALE INFERMIERISTICO E TECNICO

3° SIMPOSIO "CELLULE STAMINALI: DALLA BIOLOGIA ALLA CLINICA"

Torino, 9-12 novembre 2011
Centro Congressi Lingotto


Lp(a)
Plasminogeno
Apo B100
Apoproteina (a)

DISTRIBUZIONE DI Lp(a) IN DIABETICI (N=355) E CONTROLLI SANI (N=568)

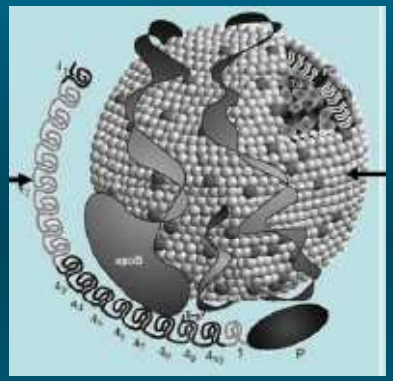


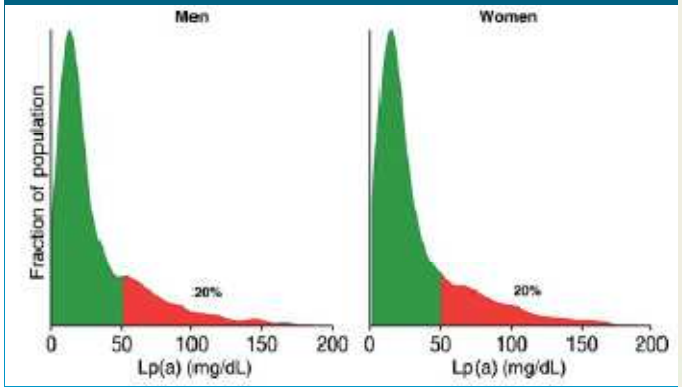
European Heart Journal (2010) 31, 2844–2853
doi:10.1093/eurheartj/ehq386

CURRENT OPINION

Lipoprotein(a) as a cardiovascular risk factor: current status

Børge G. Nordestgaard[1*], M. John Chapman[2], Kausik Ray[3], Jan Borén[4], Felicita Andreotti[5], Gerald F. Watts[6], Henry Ginsberg[7], Pierre Amarenco[8], Alberico Catapano[9], Olivier S. Descamps[10], Edward Fisher[11], Petri T. Kovanen[12], Jan Albert Kuivenhoven[13], Philippe Lesnik[2], Luis Masana[14], Zeljko Reiner[15], Marja-Riitta Taskinen[16], Lale Tokgözoglu[17], and Anne Tybjærg-Hansen[18], for the European Atherosclerosis Society Consensus Panel[†]





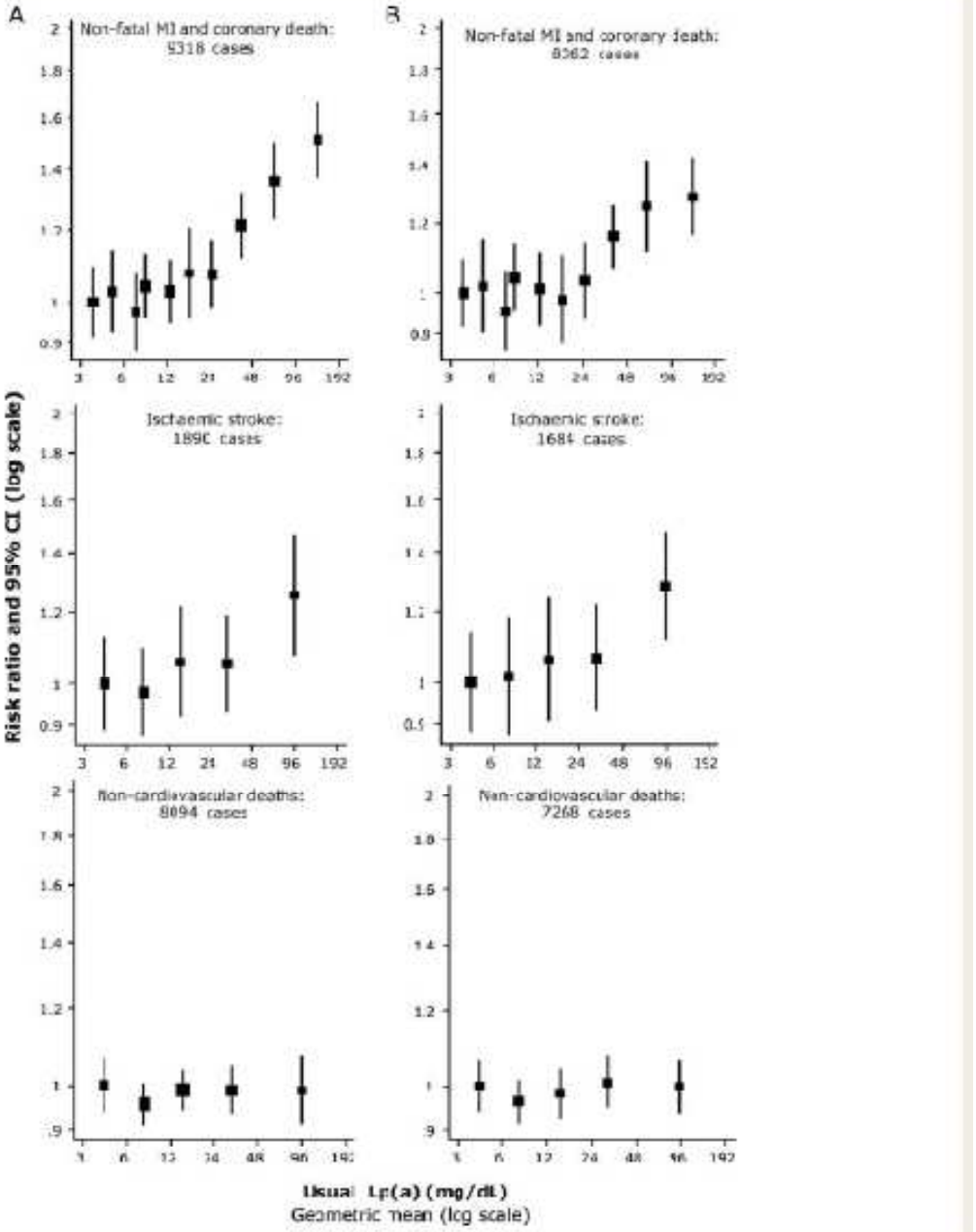
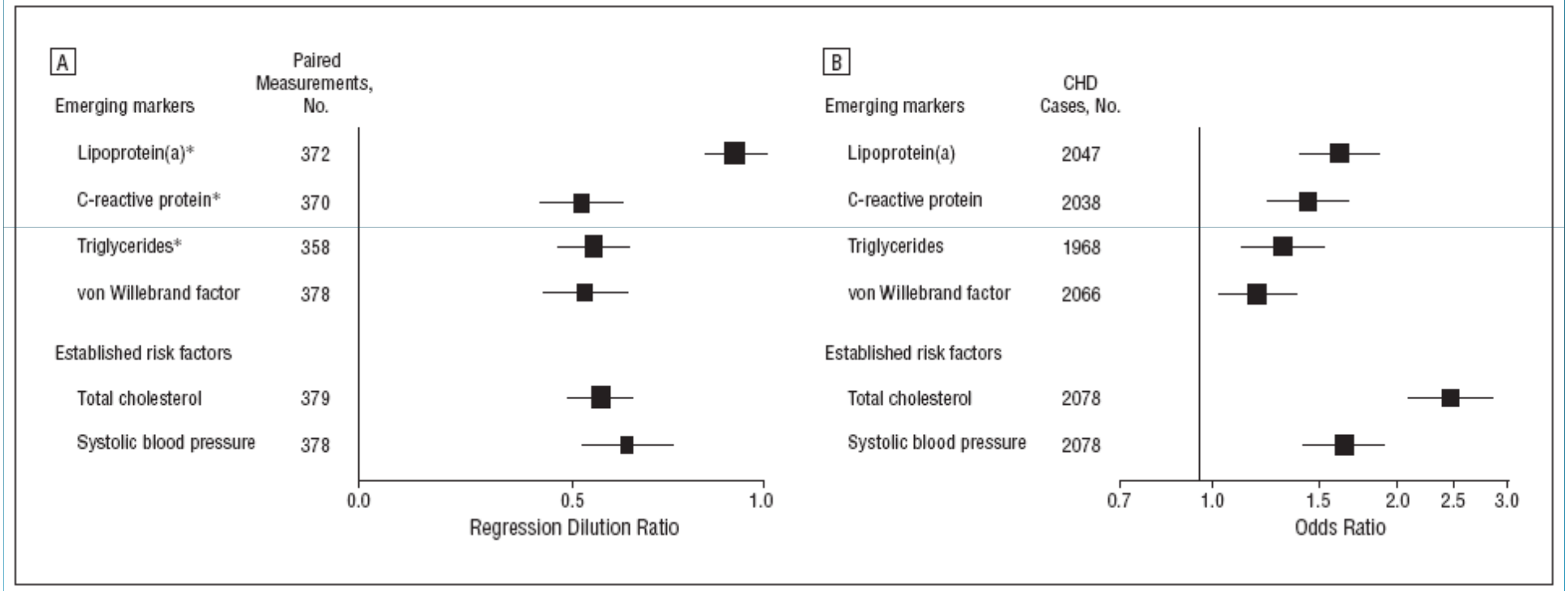


Figure 3 Risk ratios of coronary heart disease, ischaemic stroke and non-vascular death by quantiles of usual lipoprotein(a) levels. CI, confidence interval. Sizes of data markers are proportional to the inverse of the variance of the risk ratios. (A) Adjustment for age and sex only. (B) Further adjustment for systolic blood pressure, smoking status, history of diabetes, body mass index, and total cholesterol. MI, myocardial infarction. Modified from The Emerging Risk Factors Collaboration.[3]

Lipoprotein(a) Levels and Risk of Future Coronary Heart Disease

Large-Scale Prospective Data



Comparison of Lp(a) values, established cardiovascular risk factors, and emerging markers across 12 years

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genetic Variants Associated with Lp(a) Lipoprotein Level and Coronary Disease

Robert Clarke, F.R.C.P., John F. Peden, Ph.D., Jemma C. Hopewell, Ph.D., Theodosios Kyriakou, Ph.D., Anuj Goel, M.Sc., Simon C. Heath, Ph.D., Sarah Parish, D.Phil., Simona Barlera, M.S., Maria Grazia Franzosi, Ph.D., Stephan Rust, Ph.D., Derrick Bennett, Ph.D., Angela Silveira, Ph.D., Anders Malarstig, Ph.D., Fiona R. Green, Ph.D., Mark Lathrop, Ph.D., Bruna Gigante, M.D., Karin Leander, Ph.D., Ulf de Faire, M.D., Udo Seedorf, Ph.D., Anders Hamsten, F.R.C.P., Rory Collins, F.R.C.P., Hugh Watkins, F.R.C.P., and Martin Farrall, F.R.C.Path., for the PROCARDIS Consortium*

ABSTRACT

METHODS

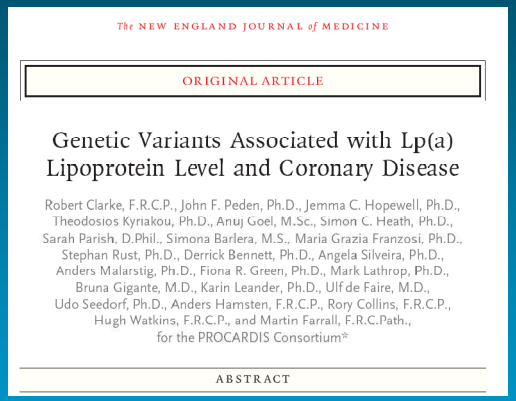
We used a novel gene chip containing 48,742 single-nucleotide polymorphisms (SNPs) in 2100 candidate genes to test for associations in 3145 case subjects with coronary disease and 3352 control subjects. Replication was tested in three independent populations involving 4846 additional case subjects with coronary disease and 4594 control subjects.

CONCLUSIONS

We identified two *LPA* variants that were strongly associated with both an increased level of Lp(a) lipoprotein and an increased risk of coronary disease. Our findings provide support for a causal role of Lp(a) lipoprotein in coronary disease.

N Engl J Med 2009;361:2518-28.

N Engl J Med 2009;361:2518-28.



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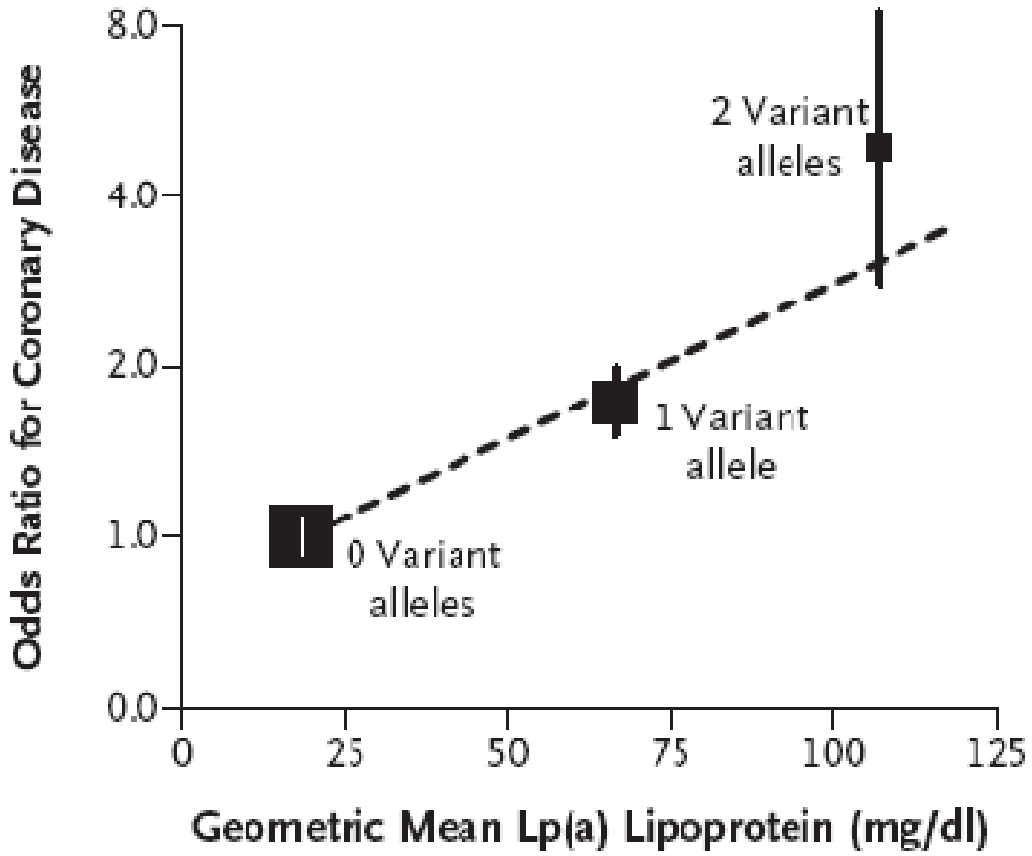

Figure 3. Association of the *LPA* Genotype Score with the Lp(a) Lipoprotein Level and the Risk of Coronary Disease in the PROCARDIS Cohort.

CONCLUSIONI

- identificazione precoce dell'Ipercolesterolemia Familiare attraverso anamnesi, esame obiettivo ed assetto lipidico esteso ai familiari di 1° grado;

- identificazione della Dislipidemia Familiare Combinata attraverso anamnesi, esame obiettivo ed assetto lipidico esteso ai familiari di 1°grado;

- valutazione vascolare periodica al fine di identificare l' arteriosclerosi in fase precoce;

ottimizzazione della terapia farmacologica

↓

LDL aferesi


GRAZIE