

# Dislipidemie rare

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# Rare Dyslipidemias

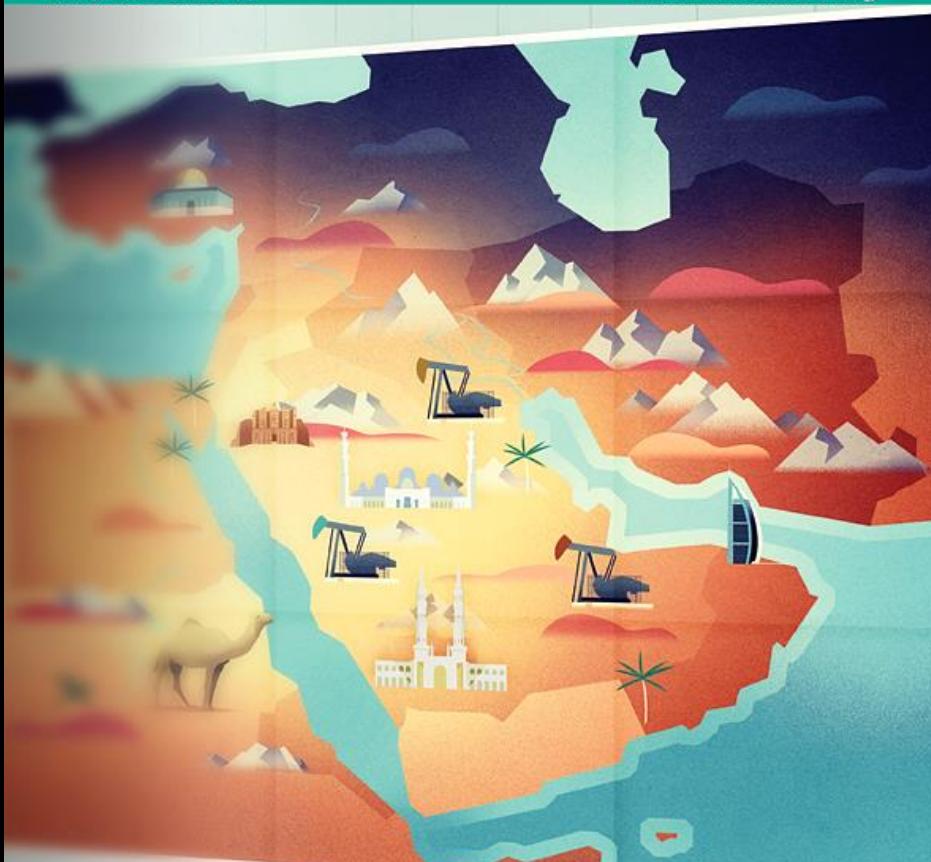
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1. Rare dyslipidemias: from phenotype to treatment
2. Rare dyslipidemias as a tool

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## Articles

Once-weekly semaglutide versus daily canagliflozin as add-on to metformin in type 2 diabetes (SUSTAIN 8)

See page 834

## Articles

Efficacy and safety of levoketoconazole in endogenous Cushing's syndrome (SONICS)

See page 855

## Review

Metabolic health in the Middle East and north Africa

See page 866

## Rare dyslipidaemias, from phenotype to genotype to management: a European Atherosclerosis Society task force consensus statement

Available online 30 September 2019

# Rare Diseases

**Table 1. Definition of 'rare' disease: Europe versus USA**

Region/Agency	Definition	Cases/100,000 of the general population
European Union/ European Medicines Agency <sup>2</sup>	Life-threatening or chronically debilitating conditions that affect no more than 5 in 10,000 people in the EU.	50
USA/ Food and Drug Administration <sup>3</sup>	Any disease or condition that (1) affects <200,000 persons in the USA, OR 2) affects >200,000 in the USA and for which there is no reasonable expectation that the cost of developing and making available in the USA a drug for such disease or condition will be recovered from sales in the USA of such a drug	64

# Rare Dyslipidemias (rare lipoprotein disorders)

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Rare monogenic disorders caused by mutations in 23 known genes

- LOF mutations in different genes may produce the same phenotype
- Different LOF mutations in the same gene may produce different phenotypes
- Contrasting mutations (LOF and GOF) in the same gene may cause opposite phenotypes

# Rare Dyslipidemias (rare lipoprotein disorders)

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## Hyperbetalipoproteinemia

LDL-C >10 mmol/L - 400 mg/dL (untreated)

LDL-C >8 mmol/L - 300 mg/dL (treated)

## Hypobetalipoproteinemia

LDL-C <1 mmol/L – 40 mg/dL

## Hypertriglyceridemia

TG>10mmol/L – 880 mg/dL

## Hypoalphalipoproteinemia

HDL-C <0.5 mmol/L – 20 mg/dL

## Hyperalphalipoproteinemia

HDL-C >2.6 mmol/L – 100 mg/dL

**Table 2. Monogenic lipoprotein disorders**

Phenotype	Disorder	Inheritance	Gene	Chr	MIM reference number(s)
↑ LDL-C  (Hyperbetalipoproteinaemia)	Familial hypercholesterolaemia	ACD	<i>LDLR</i>	19p13	143890, 606945
	Familial defective apo B-100	ACD	<i>APOB</i>	2p24	144010, 615558, 107730
	Autosomal dominant hypercholesterolaemia type 3	ACD	<i>PCSK9</i>	1p32	603776, 607786
	Autosomal recessive hypercholesterolaemia	AR	<i>LDLRAP1</i>	1p35	603813, 605747
	Sitosterolemia (phytosterolemia)	AR	<i>ABCG5</i>	2p21	210250, 605459
	Sitosterolemia (phytosterolemia)	AR	<i>ABCG8</i>	2p21	210250, 605460
	Atypical dominant hypercholesterolaemia	AD	<i>APOE</i>	19q13	107741
↓ LDL-C  (Hypobetalipoproteinaemia)	Lysosomal acid lipase deficiency	AR	<i>LIPA</i>	10q23	278000, 613497
	Abetalipoproteinaemia	AR	<i>MTTP</i>	4q23	200100, 157147
	Homozygous hypobetalipoproteinaemia	ACD*	<i>APOB</i>	2p24	144010, 615558, 107730
	Chylomicron retention disease (Anderson disease)	AR	<i>SAR1B</i>	5q31	246700, 607690
	Familial combined hypolipidaemia	ACD*	<i>ANGPTL3</i>	1p31	605019, 604774
	Hypobetalipoproteinaemia, PCSK9 deficiency	ACD*	<i>PCSK9</i>	1p32	605019, 613589, 607786
↑ TG	Monogenic chylomicronemia (formerly type 1 HLP)				
	- LPL deficiency	AR	<i>LPL</i>	8p22	609708, 238600
	- Apo C-II deficiency	AR	<i>APOC2</i>	19q13	207750, 608083
	- Apo A-V deficiency	AR	<i>APOA5</i>	11q23	145750, 144650, 606368
	- Lipase maturation factor 1 deficiency	AR	<i>LMF1</i>	16p13	246650, 611761
	- GPIHBP1 deficiency	AR	<i>GPIHBP1</i>	8q24	612757
	Infantile hypertriglyceridaemia, transient	AR	<i>GPD1</i>	12q12	614480, 138420
↓ HDL-C  (Hypoalphalipoproteinaemia)	Dysbetalipoproteinaemia (formerly type III HLP)	Complex	<i>APOE</i>	19q13	107741
	Tangier disease	ACD*	<i>ABCA1</i>	9q31	205400, 600046
↑ HDL-C  (Hyperalphalipoproteinaemia)	Apo A-I deficiency	ACD*	<i>APOA1</i>	11q23	604091, 107680
	LCAT deficiency; Fish eye disease	ACD*	<i>LCAT</i>	16q22	245900, 136120, 606967
	Cholesteryl ester transfer protein deficiency	ACD	<i>CETP</i>	16q13	143470, 118470
	Scavenger receptor B1 deficiency	ACD	<i>SCARB1</i>	12q24	610762, 601040
	Hepatic lipase deficiency	ACD	<i>LIPC</i>	15q21	614025, 151670

# Rare Dyslipidemias - Diagnosis

## Baseline lipid evaluation

- lipoprotein profile: total, low-density lipoprotein and high-density lipoprotein cholesterol and triglyceride
- apolipoproteins B and A-I
- Lipoprotein(a)

# Rare Dyslipidemias - Diagnosis

## Baseline lipid evaluation

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## Screening for secondary causes of dyslipidaemia

- diabetes: fasting glucose, glycated hemoglobin
- hypothyroidism: thyroid stimulating hormone
- liver disease: transaminases, bilirubin, alkaline phosphatase, gamma glutamyl transferase
- renal disease: serum creatinine, urinary albumin, albumin to creatinine ratio
- autoimmune diseases: serum rheumatoid factor, antinuclear antigen, C-reactive protein

# Rare Dyslipidemias - Diagnosis

## Clinical assessment

### Associated abnormalities

- hematologic: abnormal erythrocyte morphology in low LDL-C states and LCAT deficiency
- coagulation: prolonged international normalized ratio in low LDL-C states
- serum fat soluble vitamin levels: depressed in low LDL-C states
- serum pancreatic lipase: elevated in hypertriglyceridemia-associated pancreatitis
- cardiovascular: non-invasive imaging of premature atherosclerosis in coronary, extracranial carotid arteries and peripheral arteries in several conditions
- gastrointestinal and hepatic: abdominal ultrasound for fatty liver in low LDL-C states, hepatosplenomegaly in monogenic chylomicronemia

## Genetic analysis

Diagnostic targeted sequencing panel or exome slice for dyslipidaemia genes

- causative genes listed in Table 2

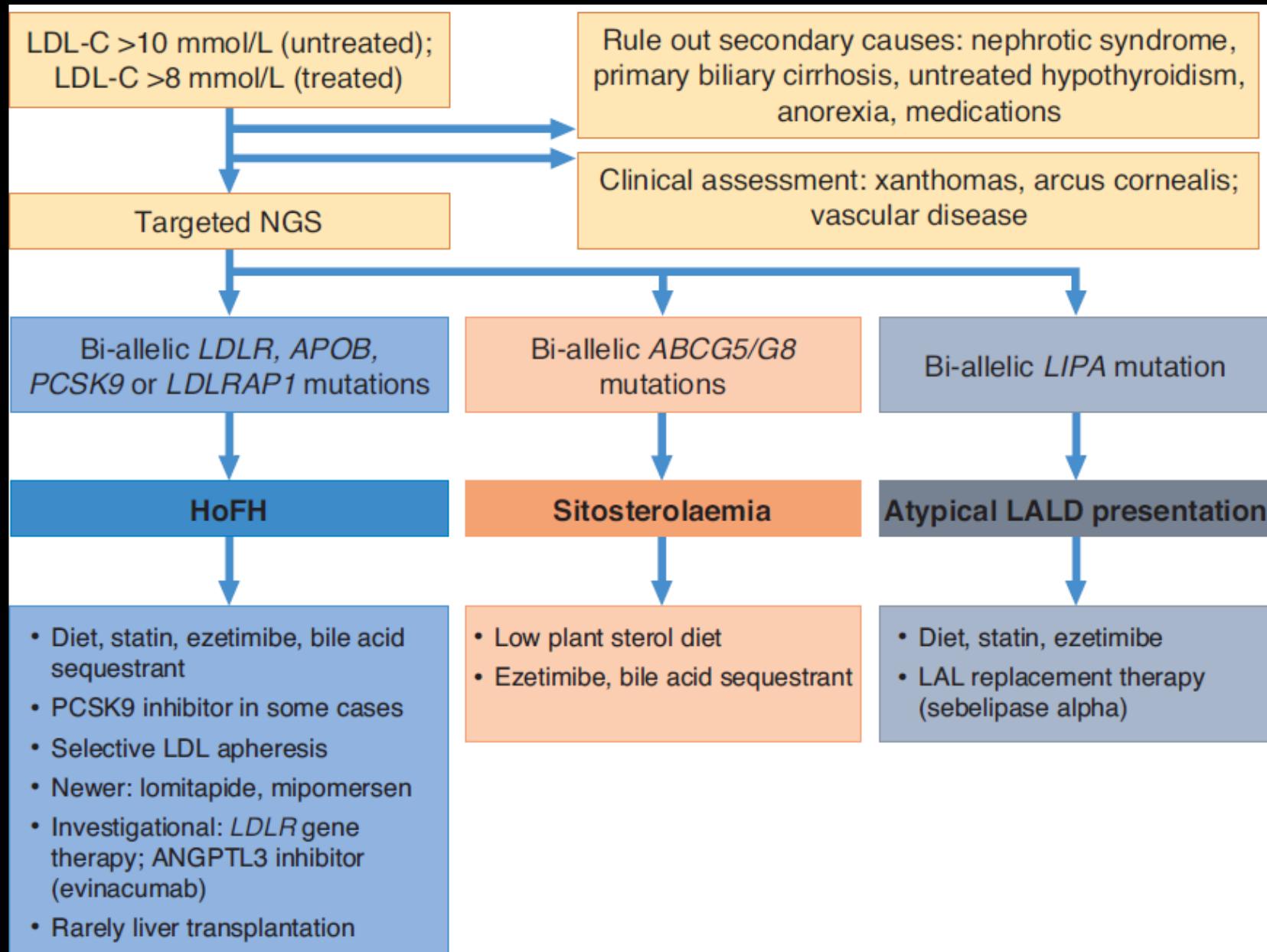
# Rare Dyslipidemias - Diagnosis

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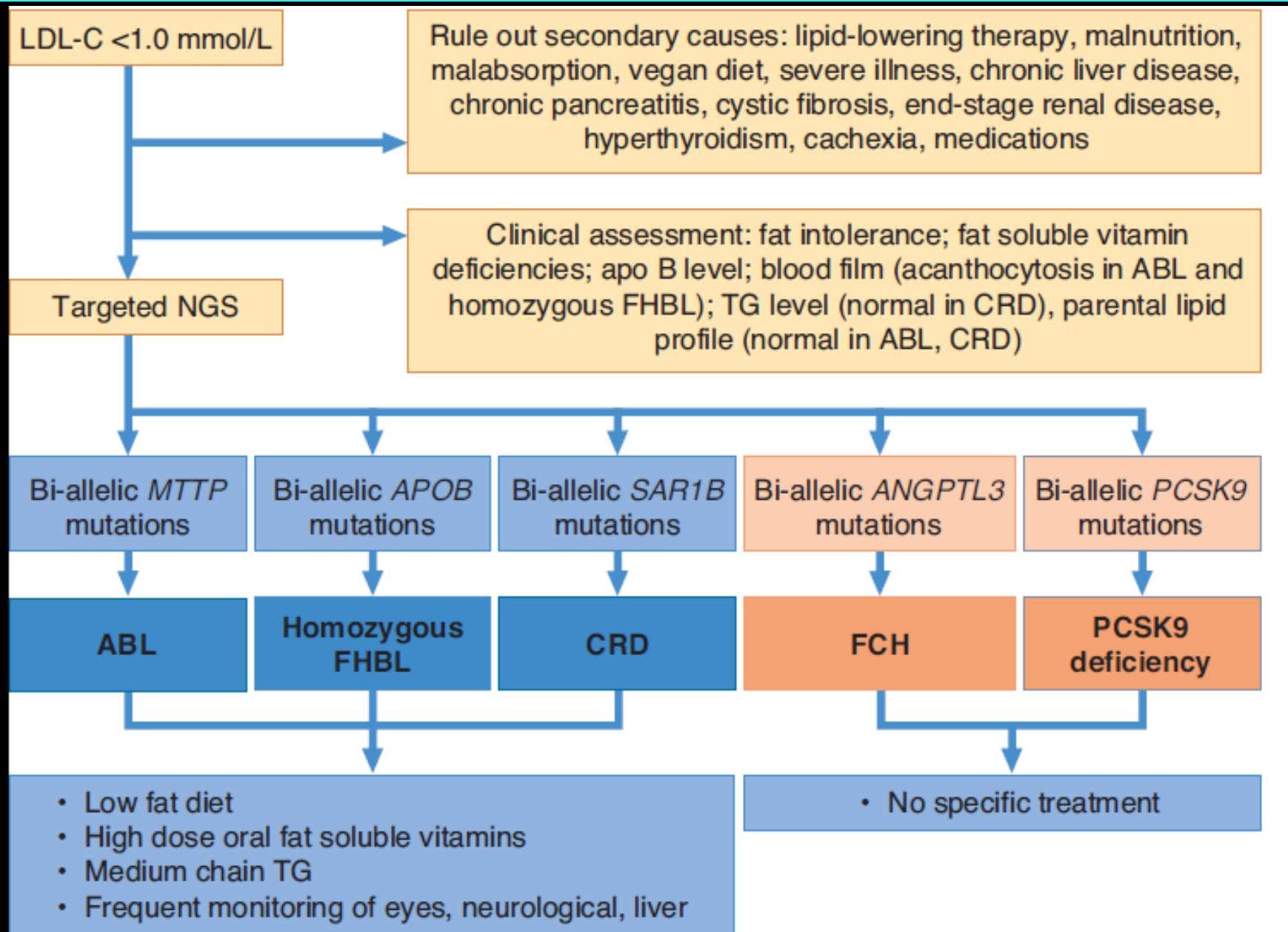
**Specialized research lipid biochemistry (not essential; confirmatory or for academic interest)**

- serum or plasma plant sterols to confirm sitosterolaemia
- post-heparin plasma lipolytic assay to confirm lipoprotein lipase deficiency
- serum or plasma lysosomal acid lipase to confirm lysosomal acid lipase deficiency
- serum cholesterol efflux capacity in HDL-C deficiency states

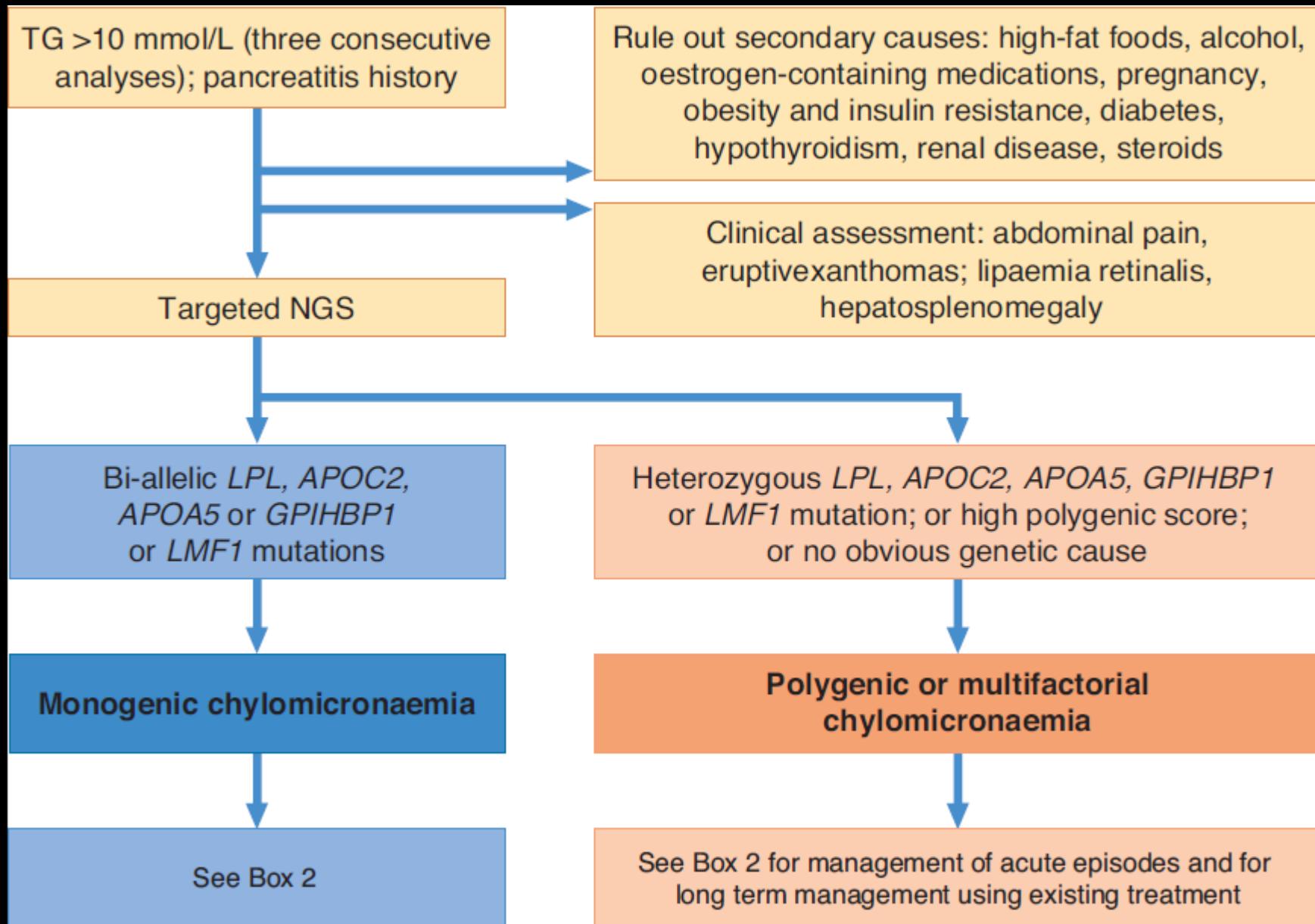
# Rare Dyslipidemias - Hyperbetalipoproteinemia



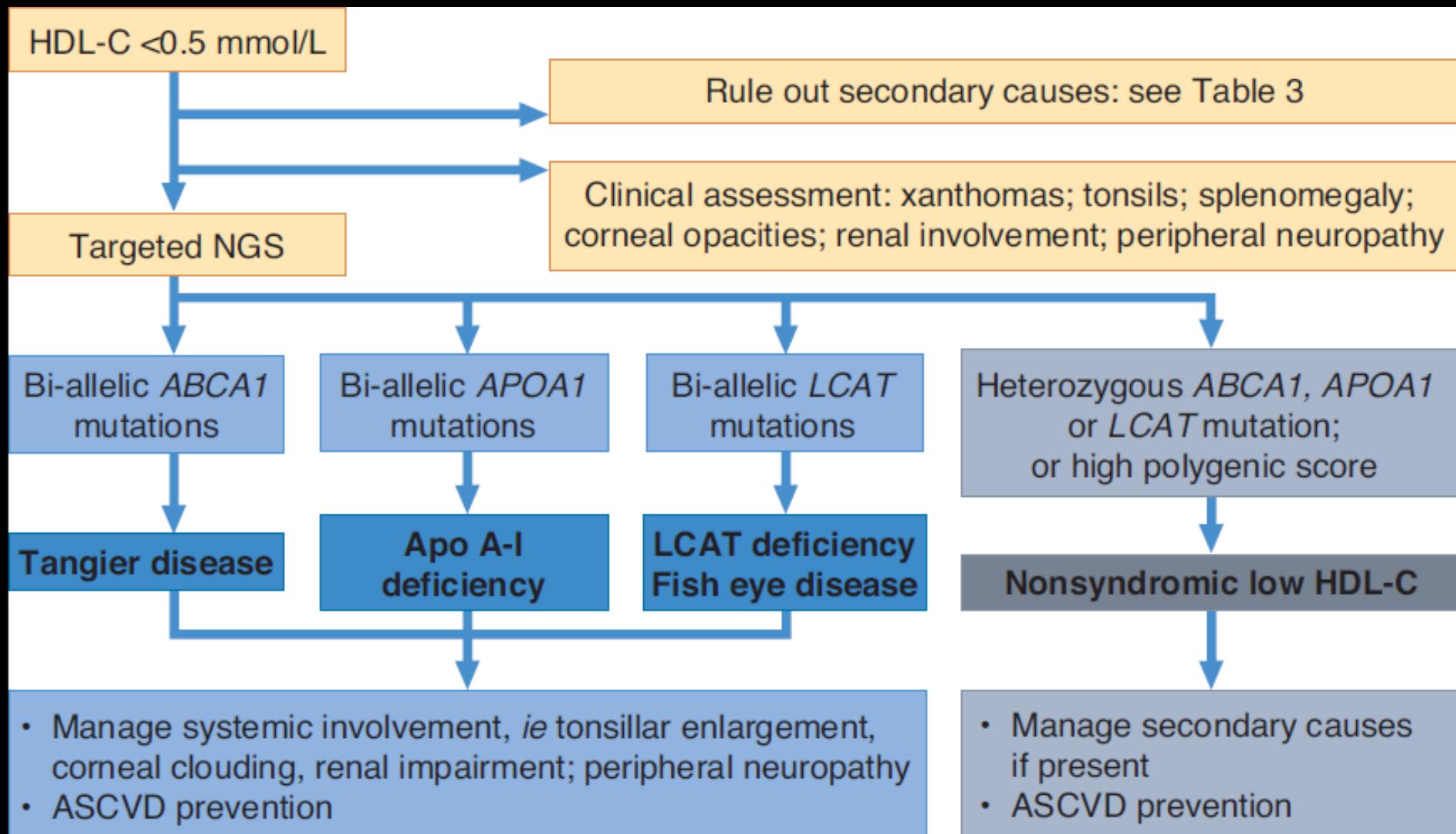
# Rare Dyslipidemias - Hypobetalipoproteinemia



# Rare Dyslipidemias - Hypertriglyceridemia



# Rare Dyslipidemias - Hypoalphalipoproteinemia



# Rare Dyslipidemias – Unmet needs

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## underdiagnosis and undertreatment

- cost of and access to current diagnostic modalities and emerging therapies
- lack of information about prevalence, pathophysiology, and outcomes
- difficulties in running studies on hard outcomes (entire global population with a rare dyslipidaemia may number in the few hundreds or thousands)
- lack of effective treatments for certain conditions

Referral of patients to specialized centers  
Development of collaborative registries

# Novel Therapeutics for Rare Dyslipidemias

Indication	Name	Mechanism of action	Stage
HoFH	lomitapide	Oral MTP inhibitor	approved in North America, Europe, Latin America and Asia
HoFH	mipomersen	Anti-APOB antisense	approved in US, Japan
HoFH	AAV8.TBG.hLDLR (RGX-501)	LDLR gene therapy	phase 1
HoFH; monogenic chylomicronaemia	evinacumab	Anti-ANGPTL3 antibody	phase 2-3
monogenic chylomicronaemia	alipogene tiparvovec	LPL gene therapy	development suspended
monogenic chylomicronaemia	volanesorsen	Anti-APOC3 ASO	approved in Europe
Low HDL-C	CSL-112/CER-001	Synthetic HDL infusion	phase 3
LCAT deficiency	ACP-501	Recombinant LCAT	phase 1
LAL deficiency	sebelipase alfa	LAL replacement	approved in North America, Europe, Latin America and Asia

# Rare Dyslipidemias

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# Monogenic HDL Disorders

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## *Low HDL*

Apolipoprotein A-I deficiency (OMIM 107680)

Tangier Disease (OMIM 205400)

## LCAT Deficiency Syndromes

Familial LCAT deficiency (FLD) (OMIM 245900)

Fish Eye Disease (FED) (OMIM 136120)

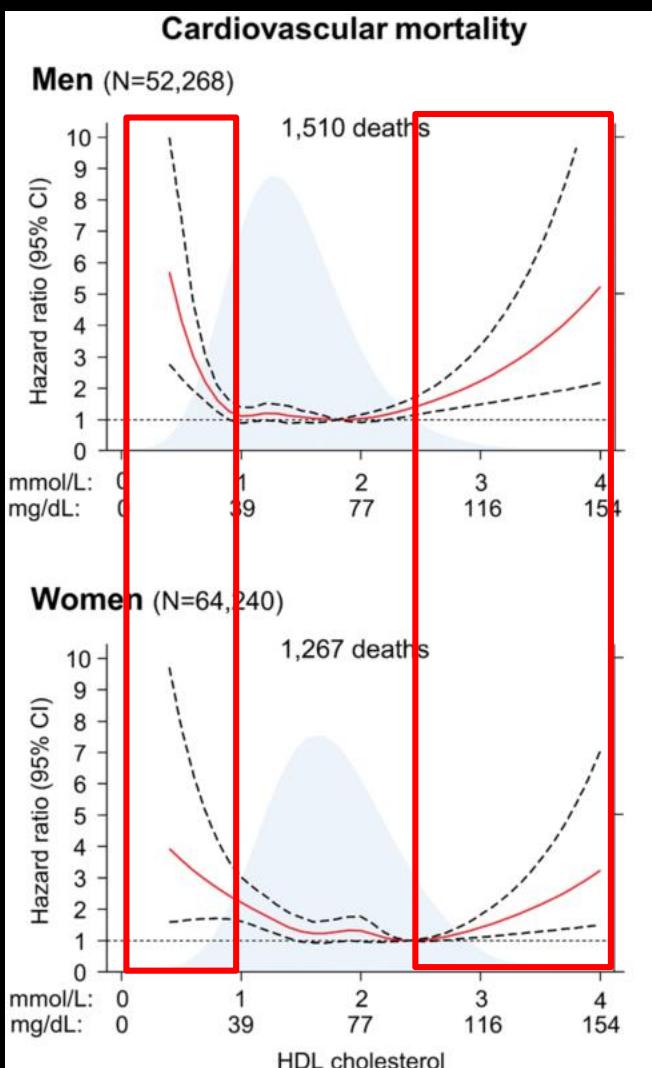
## *High HDL*

CETP deficiency (OMIM 607322)

SR-BI deficiency (OMIM 614025)

# HDL-C and Cardiovascular Mortality

## Copenhagen Studies



# HDL and atherosclerosis

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*insights from inherited HDL disorders*

# Genetic HDL disorders in Italy

ApoA-I deficiency (OMIM #107680)

103 carriers (3 mutations)

2 HOZ and 101 HEZ

LCAT deficiency (OMIM #245900, 136120)

89 carriers (28 mutations)

25 HOZ and 64 HEZ

CETP deficiency (OMIM #607322)

8 carriers (3 mutations)

1 HOZ and 7 HEZ



GGP02264

GGP06132

GGP08052

GGP14125

PRIN2005

Cariplo 2003-1743

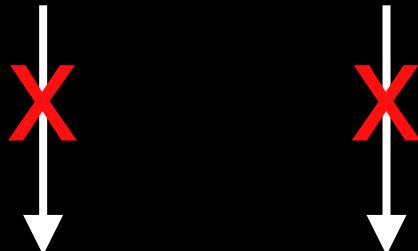
Cariplo 2009-2576

Cariplo 2011-0628

# Genetic LCAT Deficiencies

Unesterified Cholesterol

HDL      LDL



Cholester~~yl~~ Ester



FLD

(Familial LCAT Deficiency)

Unesterified Cholesterol

HDL      LDL



HDL-CE      LDL-CE



FED

(Fish-Eye Disease)

# Genetic LCAT Deficiency in Italy

## Plasma Lipids/lipoproteins

Number of mutant <i>LCAT</i> alleles	Two (n=18)	One (n=64)	Zero (n=20)	Trend <i>P</i> *
TC (mg/dl)	160.7 ±20.8	162.4 ±7.2	196.7 ±9.2	0.344
UC (mg/dl)	125.1 ±17.5	49.3 ±2.2	50.4 ±4.1	<0.001
LDL-C (mg/dl)	102.9 ±16.5	97.2 ±6.6	114.6 ±8.5	0.578
HDL-C (mg/dl)	10.4 ±1.6	40.0 ±2.0	51.4 ±2.9	<0.001
TG (mg/dl)	242.4 ±37.5	125.1 ±8.6	118.8 ±30.3	<0.001
ApoA-I (mg/dl)	44.8 ±3.8	101.8 ±3.6	131.4 ±5.0	<0.001
ApoA-II (mg/dl)	10.4 ±1.4	29.4 ±1.0	34.3 ±1.6	<0.001
ApoB (mg/dl)	60.7 ±11.7	90.0 ±4.2	93.9 ±6.1	0.004

# Genetic LCAT Deficiency in Italy

## Plasma Lipids/lipoproteins

Carriers of 2 mutant <i>LCAT</i> alleles	FLD (n=11)	FED (n=7)	P
TC (mg/dl)	167.6 ±84.1	148.0 ±95.7	0.654
UC (mg/dl)	153.2 ±70.6	73.7 ±41.9	0.017
LDL-C (mg/dl)	106.6 ±69.8	96.0 ±70.6	0.759
HDL-C (mg/dl)	8.7 ±5.2	13.5 ±7.8	0.135
TG (mg/dl)	269.1 ±169.2	193.5 ±129.1	0.329
ApoA-I (mg/dl)	37.9 ±7.3	57.5 ±19.1	0.007
ApoA-II (mg/dl)	7.7 ±4.1	15.3 ±4.9	0.003
ApoB (mg/dl)	41.4 ±23.1	90.2 ±57.5	0.021

Mean ±SD

# Genetic LCAT Deficiency in Italy

## Cholesterol Esterification

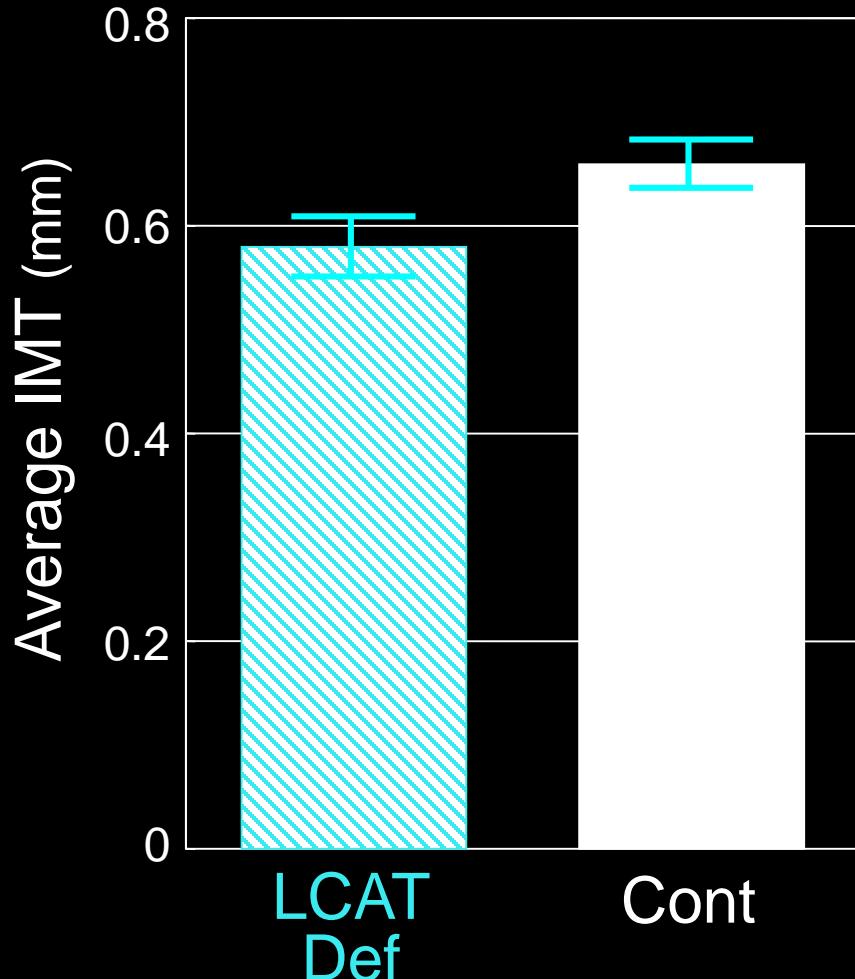
Carriers of 2 mutant <i>LCAT</i> alleles	FLD (n=11)	FED (n=7)	P
UC/TC	0.93 ±0.08	0.53 ±0.15	<0.001
CER (nmol/ml/hr)	0	44.6 ±8.9	<0.001
LCAT act (nmol/ml/hr)	0	0	
LCAT (μg/ml)	1.3 ±0.8	2.2 ±0.5	0.018

Mean ±SD

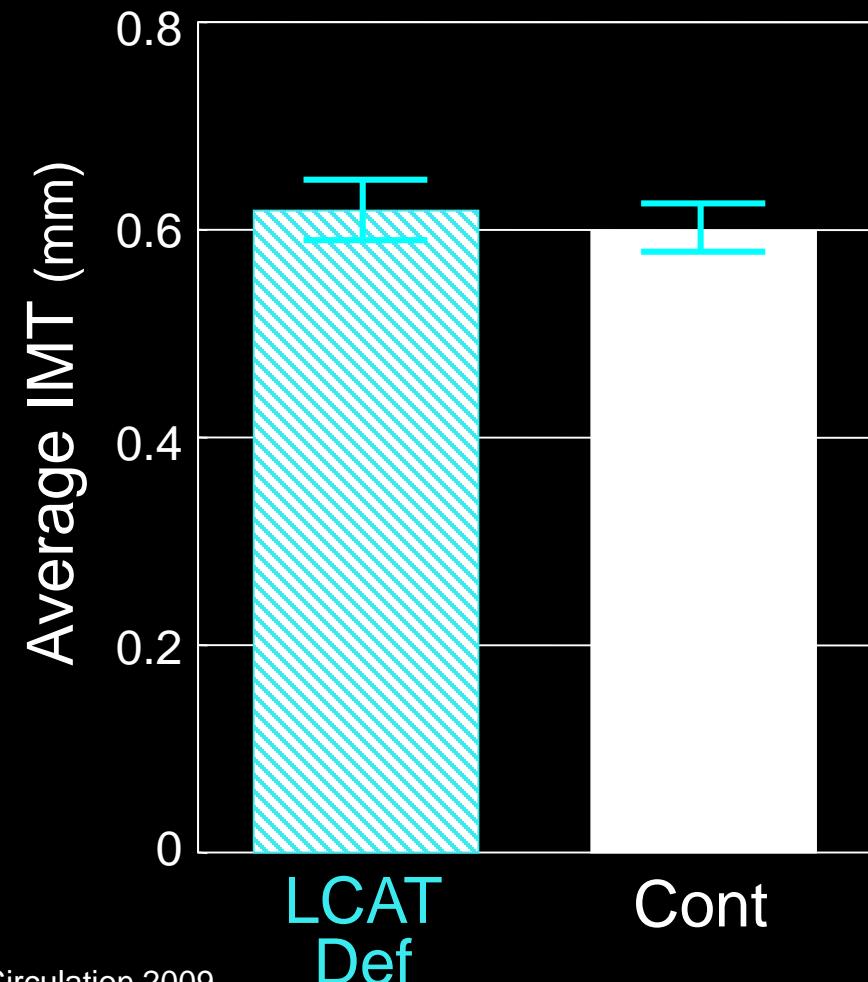
# Genetic LCAT Deficiency

## Carotid Intima-Media Thickness

Italians



Dutch



Calabresi et al, Circulation 2009  
Hovingh et al, Circulation 2005

# Genetic LCAT Deficiency

## Carotid Intima-Media Thickness

### Dutch and Italian Carriers

	FLD Carriers	FED Carriers	Controls
n.	33	41	280
Italian/Dutch	26/7	9/32	113/167
Gender (M, %)	18 (54.5%)	27 (65.9%)	152 (54.3%)
Age (y)	$44.8 \pm 19.3$	$44.5 \pm 13.8$	$43.9 \pm 13.3$

Images recorded in Amsterdam and Milano  
Single reader (Samuela Castelnuovo-Milano)

# Genetic LCAT Deficiency

## Carotid Intima-Media Thickness

### Dutch and Italian Carriers

	FLD Carriers	FED Carriers	Controls
Total Cholesterol (mg/dL)	168 ± 39	186 ± 53	200 ± 39
LDL Cholesterol (mg/dL)	102 ± 35	124 ± 47	123 ± 35
HDL Cholesterol (mg/dL)	42 ± 13	38 ± 14	58 ± 16
Triglycerides (mg/dL)	97 (77; 144)	100 (81; 146)	86 (60; 123)
Non-HDL Cholesterol (mg/dL)	126 ± 41	148 ± 51	142 ± 40
Ratio LDL-C/HDL-C	2.2 (1.9; 3.4)	3.4 (2.2; 4.2)	2.1 (1.6; 2.8)

# Genetic LCAT Deficiency

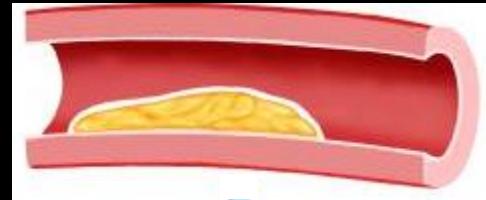
## Carotid Intima-Media Thickness

### Dutch and Italian Carriers

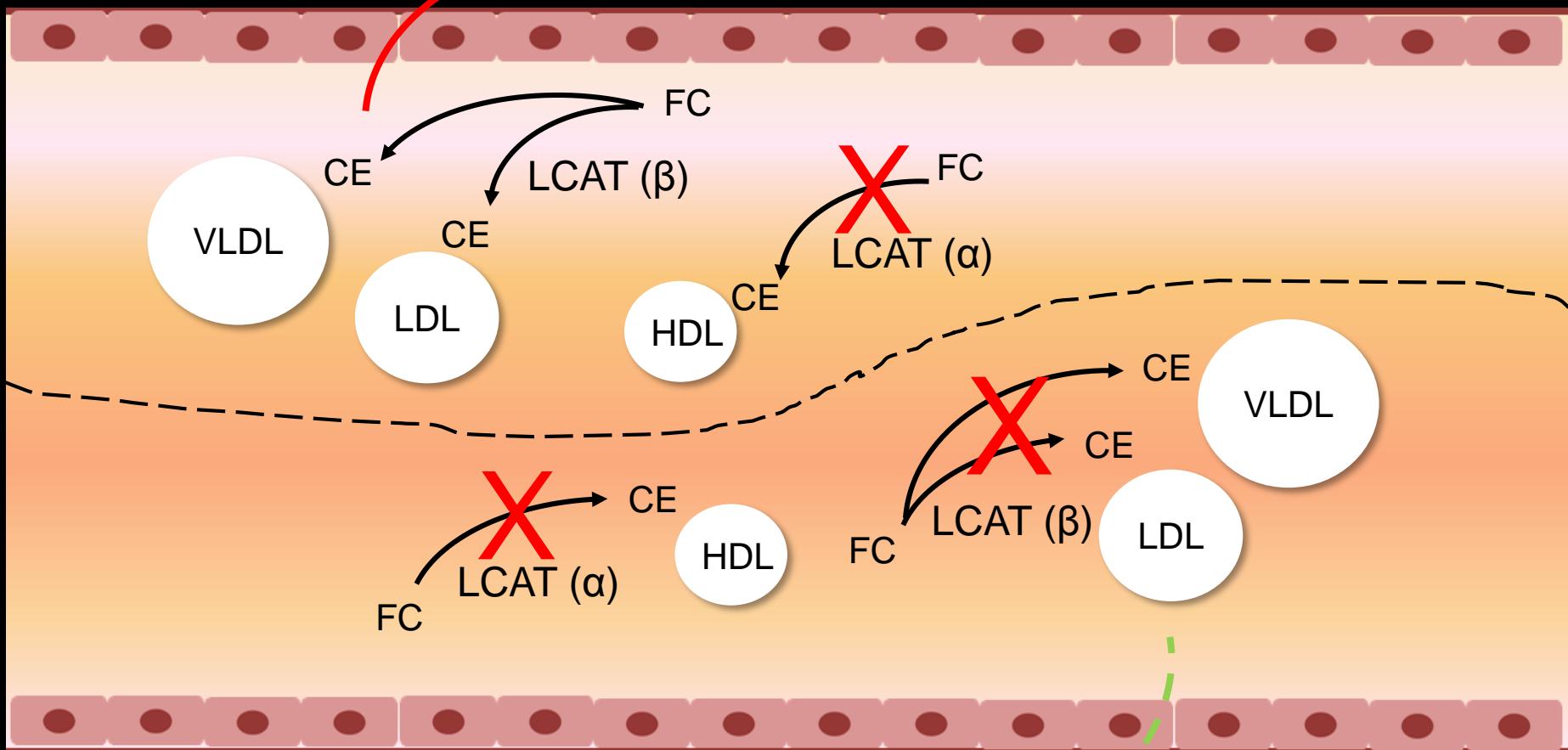


\* $P<0.001$  vs FLD and  $P=0.050$  vs controls; \*\* $P=0.028$  vs Controls, adjusted for age and sex, BMI, smoking, hypertension, family history of cardiovascular disease, total cholesterol, HDL-cholesterol, and triglycerides

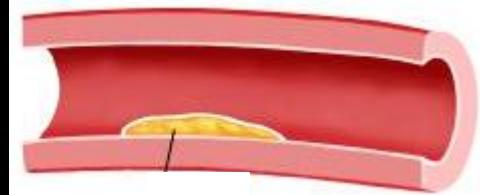
More prone to atherosclerosis



## Fish-Eye Disease (FED)



## Familial LCAT deficiency (FLD)



Less prone to atherosclerosis

# Acknowledgments

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