



Per la promozione della ricerca sulle malattie da arteriosclerosi



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

Endorsed by



## DYSBETALIPOPROTEINAEMIA

Giuseppe Danilo Norata  
University of Milan, Italy



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# DYSBETALIPOPROTEINAEMIA

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- Hyperlipoproteinemia Type III
- Broad Beta Disease
- Familial Dysbetalipoproteinemia
- Remnant Removal Disease



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# DYSBETALIPOPROTEINAEMIA

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1. Clinical Phenotype

2. Genetics

3. Consequences on lipids/lipoprotein metabolism

4. Remnant particles and atherosclerosis

5. Pharmacology



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# 1.Clinical Phenotype

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- Hyperlipidemia

**Cholesterol > 7 mmol/L (270 mg/dL)**

**Triglyceride > 4 mmol/L (350 mg/dL)**

**VLDL-C to total cholesterol ratio > 0.3**



# 1.Clinical Phenotype

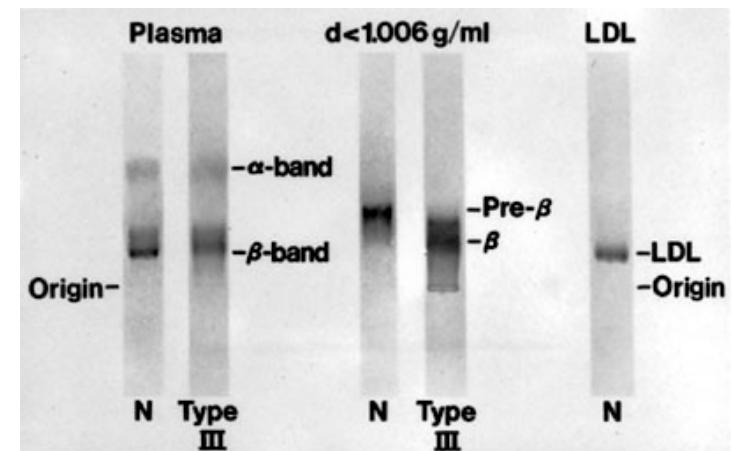
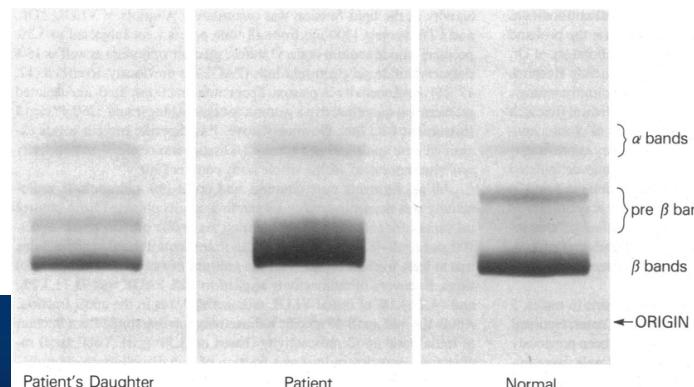
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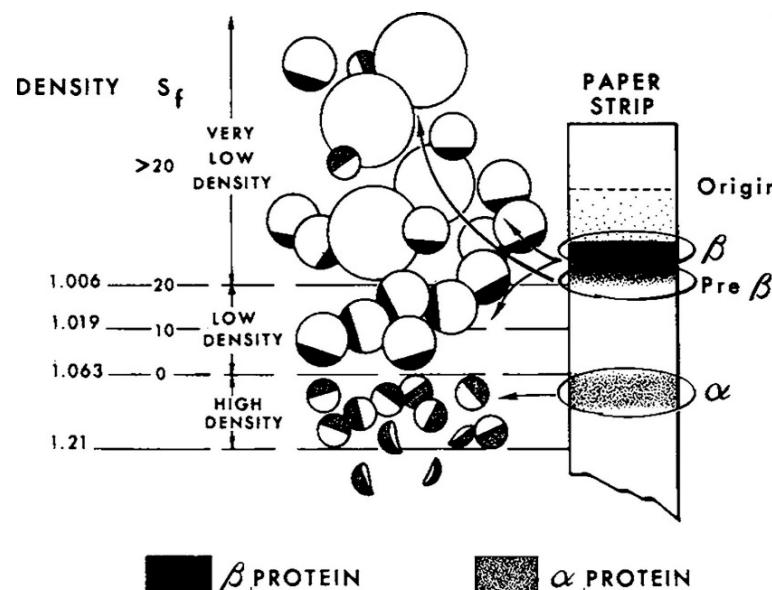
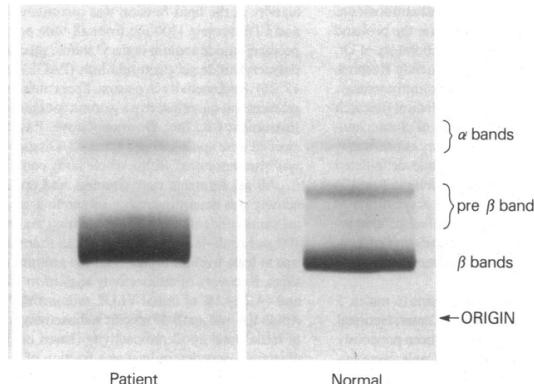
## Lipoprotein Electrophoresis



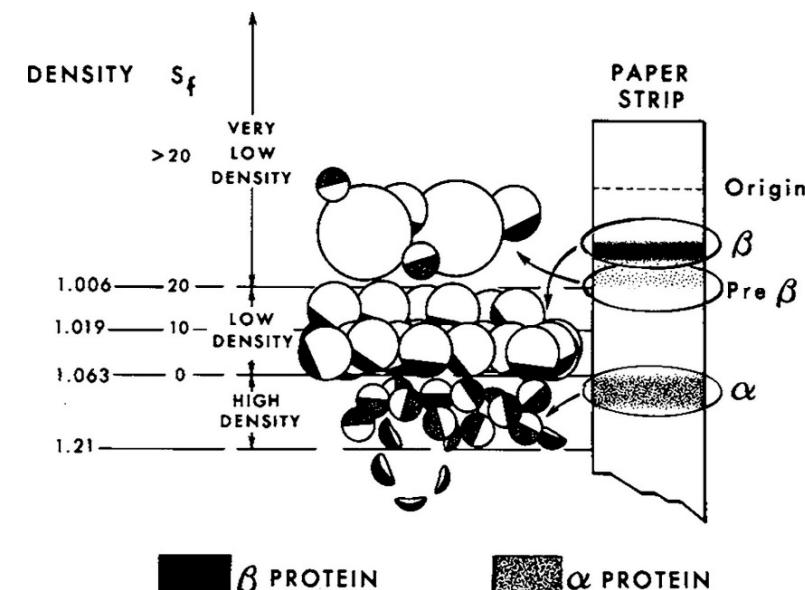
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# 1.Clinical Phenotype

Broad band disease



Type III-hyperlipidemia



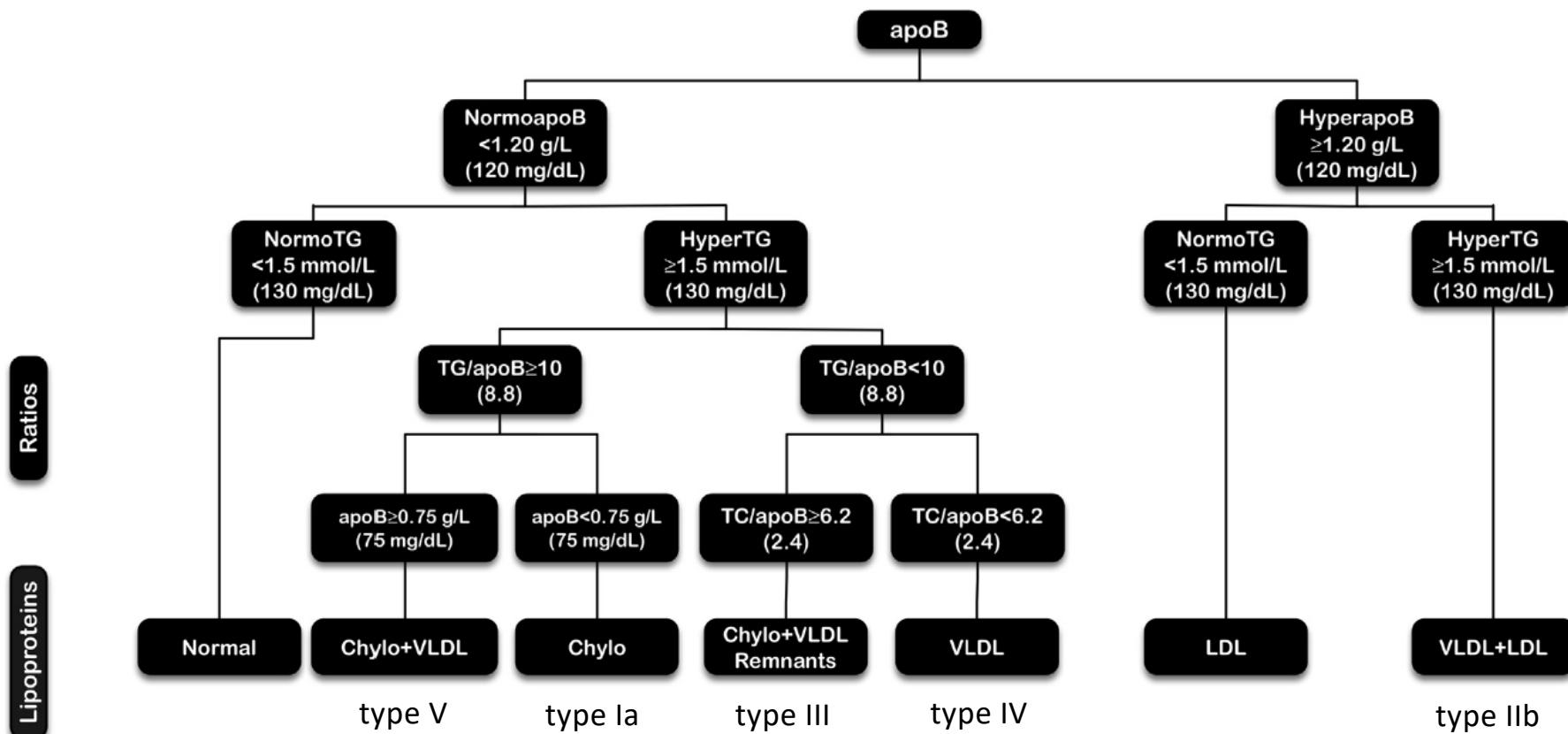
Normal

# 1.Clinical Phenotype

Original Article

## The spectrum of type III hyperlipoproteinemia

Allan D. Sniderman, MD\*, Jacqueline de Graaf, MD, George Thanassoulis, MD,  
André J. Tremblay, PhD, Seth S. Martin, MD, Patrick Couture, MD

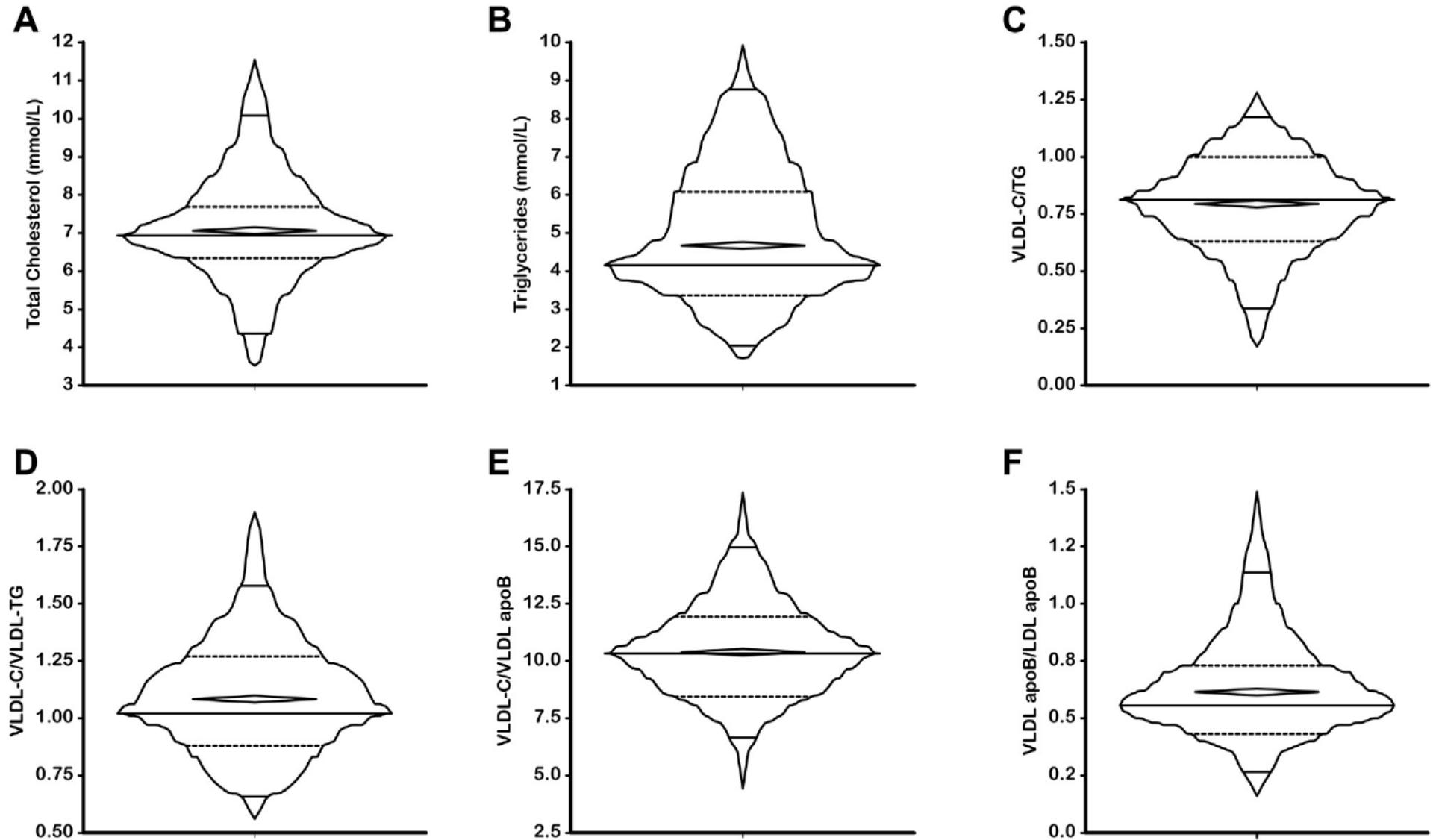


# 1.Clinical Phenotype

**Table 2** Lipid and lipoprotein lipid levels in hypertriglyceridemic subjects

	Normal N = 440	Type I N = 55	Type IIB N = 802	Type III N = 49	Type IV N = 411	Type V N = 34
Characteristics	Median (25th–75th)	Median (25th–75th)	Median (25th–75th)	Median (25th–75th)	Median (25th–75th)	Median (25th–75th)
Characteristics	-	Chylo	VLDL + LDL	Chylo + VLDL remnants	VLDL	Chylo + VLDL
Age (y)	28.0 (11.8–46.2)	31.6 (22.4–40.2)	48.2 (39.5–57.4)*,†	44.4 (39.2–52.4)*,†	42.9 (32.2–52.2)*,†,‡	42.7 (32.9–49.4)*,†
Gender (M/F)	240/200	42/13	539/263	39/10	291/120	30/4
Cholesterol (mmol/L)						
Total	5.01 (4.41–5.60)	6.18 (4.56–9.54)*	6.61 (5.99–7.41)*	6.93 (6.28–7.81)*	4.94 (4.47–5.44)*,†,§	7.71 (6.07–9.65)*,†,§,
VLDL	0.35 (0.22–0.46)	0.72 (0.36–1.34)*	1.22 (0.84–1.81)*,†	3.41 (2.46–4.26)*,†,‡	1.02 (0.74–1.67)*,†,§	3.01 (1.41–6.14)*,†,‡,
LDL	3.42 (2.92–3.87)	0.56 (0.39–0.85)*	4.18 (3.52–4.90)*,†	2.11 (1.66–2.69)*,†,‡	2.70 (2.15–3.27)*,†,‡,§	1.16 (0.9–1.57)*,†,§,
HDL	1.24 (1.04–1.46)	0.42 (0.37–0.57)*	0.91 (0.78–1.08)*,†	0.87 (0.76–1.07)*,†	0.87 (0.72–1.04)*,†	0.61 (0.53–0.68)*,†,§,
Triglyceride						
Total	1.01 (0.78–1.22)	17.0 (12.2–30.5)*	2.7 (2.00–4.15)*,†	4.16 (3.35–6.08)*,†	2.48 (1.84–3.88)*,†	13.9 (11.5–20.7)*,†,‡,§,
Chylo	0.27	15.4 (10.2–27.8)	3.00 (1.32–6.45)*	2.88 (1.25–4.00)*	1.53 (0.72–3.31)*	14.0 (8.7–17.5)*,†,‡,§,
VLDL	0.54 (0.35–0.71)	1.65 (0.97–3.06)*	1.98 (1.35–3.19)*	2.89 (2.13–4.03)*,†	1.85 (1.26–3.16)*,§	7.37 (2.88–12.5)*,†,‡,§,
LDL	0.23 (0.18–0.28)	0.36 (0.26–0.41)*	0.44 (0.36–0.55)*,†	0.34 (0.29–0.46)*,‡	0.31 (0.26–0.37)*,‡	0.43 (0.34–0.52)*,†,
HDL	0.21 (0.18–0.25)	0.38 (0.33–0.58)*	0.26 (0.22–0.32)*,†	0.37 (0.31–0.42)*,†,‡	0.28 (0.23–0.34)*,†,§	0.49 (0.43–0.58)*,†,§,
Apolipoprotein B (g/L)						
Total	0.99 (0.87–1.10)	0.54 (0.43–0.66)*	1.42 (1.31–1.58)*,†	0.91 (0.77–1.07)*,‡	1.06 (0.95–1.13)*,†,‡,§	0.94 (0.85–1.08)*,‡
VLDL	0.09 (0.07–0.12)	0.14 (0.06–0.20)	0.22 (0.16–0.30)*,†	0.31 (0.25–0.37)*,†,‡	0.18 (0.14–0.26)*,†,‡,§	0.36 (0.24–0.49)*,†,‡,
LDL	0.89 (0.78–1.00)	0.41 (0.30–0.48)*	1.19 (1.08–1.35)*,†	0.55 (0.47–0.68)*,†,‡	0.85 (0.74–0.94)*,‡,§	0.59 (0.48–0.73)*,†,‡,
Ratios						
VLDL-C/TG	0.34 (0.27–0.39)	0.03 (0.01–0.07)*	0.43 (0.39–0.49)*,†	0.81 (0.62–1.01)*,†,‡	0.41 (0.36–0.47)*,†,‡,§	0.23 (0.07–0.43)*,†,‡,§,
VLDL-C/VLDL-TG	0.63 (0.53–0.72)	0.39 (0.33–0.49)*	0.60 (0.52–0.70)*	1.02 (0.86–1.29)*,†,‡	0.55 (0.48–0.63)*,†,‡,§	0.46 (0.40–0.58)*,†,‡,§
VLDL-C/VLDL apoB	3.54 (2.50–4.63)	6.09 (3.85–9.43)*	6.04 (4.87–7.29)*,†	10.3 (8.4–12.0)*,‡	5.96 (5.00–7.21)*,†,§	8.53 (5.56–13.7)*,†,‡,§
VLDL apoB/LDL apoB	0.11 (0.08–0.15)	0.28 (0.16–0.48)*	0.17 (0.12–0.25)*,†	0.56 (0.43–0.73)*,†,‡	0.21 (0.16–0.33)*,†,‡,§	0.63 (0.38–0.94)*,†,‡,

# 1.Clinical Phenotype



# 1.Clinical Phenotype

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- **Xanthoma striata palmaris**



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# DYSBETALIPOPROTEINAEMIA

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**1. Clinical Phenotype**

**2. Genetics**

**3. Consequences on lipids/lipoprotein metabolism**

**4. Remnant particles and atherosclerosis**

**5. Pharmacology**



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## 2. Genetics

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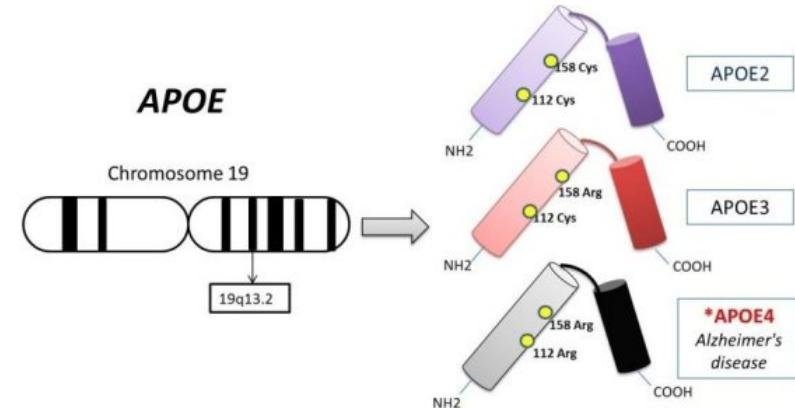
- Apolipoprotein E is the key gene

-ApoE2/E2 Homozigosity

1% in the population but only 1:5000-1:10.000 display Type III hyperlipidemia.

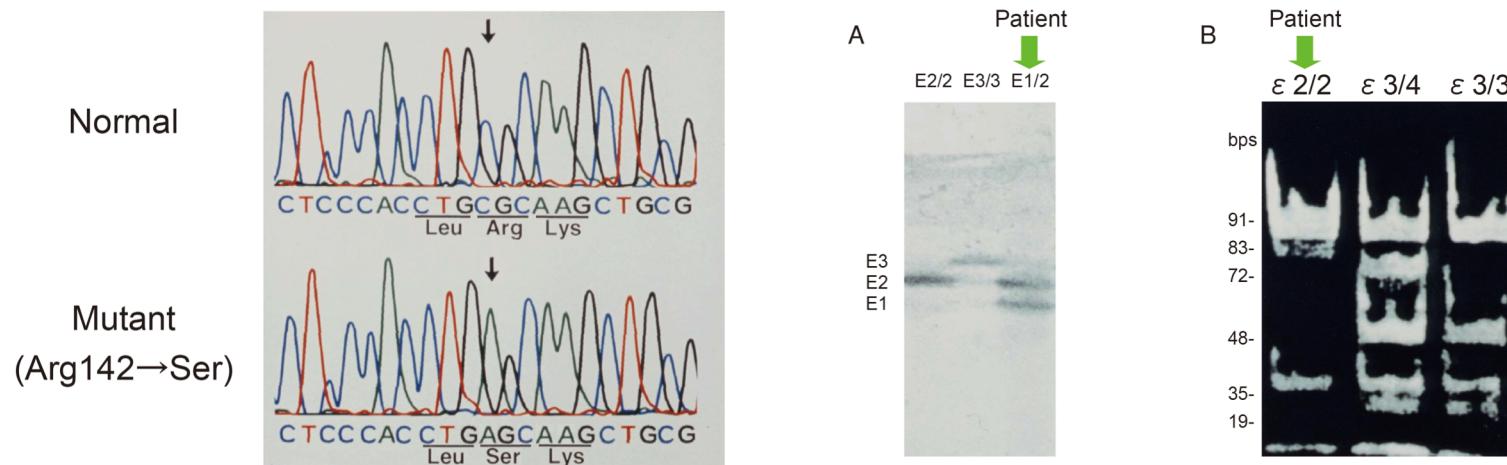
Concomitance of a second defect in lipoprotein metabolism or hypothyroidism, obesity, glucose intolerance, estrogen deficiency.

Men more susceptible (adulthood), women only after menopause



## 2. Genetics

-Compound Heterozygotes for a Novel Mutation, Apo E1 Nagoya (Arg142Ser) and Apo E2 (Arg158Cys), with Severe Type III Hyperlipoproteinemia and Familial Hypercholesterolemia  
Sakuma N et al. Journal of Atherosclerosis and Thrombosis;2014:983-988.



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Sakuma N et al. Journal of Atherosclerosis and Thrombosis;2014:983-988.

-Effects of the absence of apolipoprotein E on lipoproteins, neurocognitive function, and retinal function. Mak AC et al JAMA Neurol 2014;71:1228-36.

(Table 2). A homozygous 1-bp frameshift deletion was identified in *APOE* exon 4 (c.291delG, p.E97fs) at chr19: 45411844 (GenBank NT\_011109.16), predicting a change of residues 97 and 98 followed by a stop codon. Sanger sequencing confirmed the

Sample	Protein, mg/dL	TG, mg/dL	Cholesterol, mg/dL	
			Total	Unesterified (%)
<b>VLDL</b>				
Proband	151	408.9	621.1	181.1 (29.2)
Mother	20	34.2	7.9	3.6 (45.1)
Control	27	47.6	16.1	6.6 (40.7)
<b>IDL</b>				
Proband	20	31.1	54.8	15.3 (28.0)
Mother	11	8.3	13.5	4.7 (34.8)
Control	6	5.7	6.8	2.5 (37.5)
<b>LDL</b>				
Proband	27	12.2	31.6	11.5 (36.3)
Mother	73	32.8	94.5	27.0 (28.6)
Control	68	15.6	110.9	32.3 (29.2)
<b>HDL</b>				
Proband	117	19.5	59.0	15.8 (26.8)
Mother	114	15.2	44.8	9.7 (21.6)
Control	104	11.7	52.8	10.2 (19.2)

Figure 1. Xanthomas of a Patient With Homozygous Apolipoprotein E Deficiency



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3. Consequences on lipids/lipoprotein metabolism

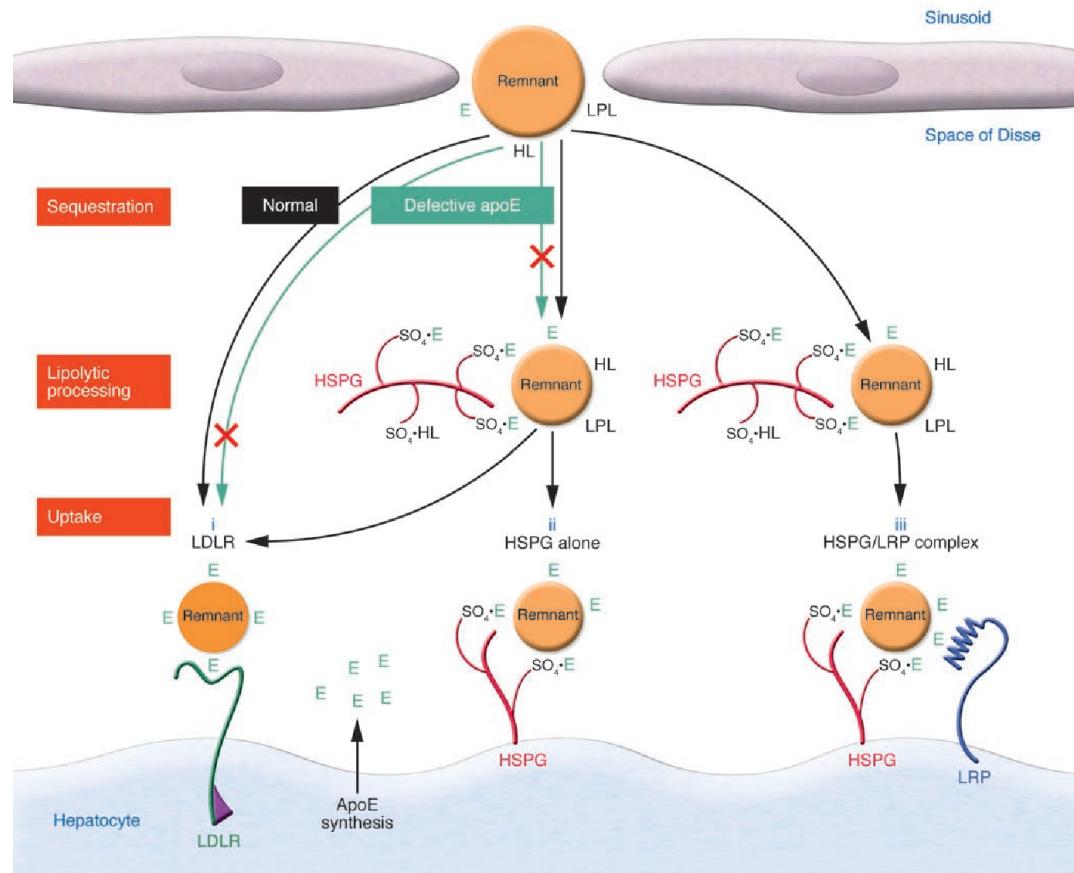
4. Remnant particles and atherosclerosis

5. Pharmacology



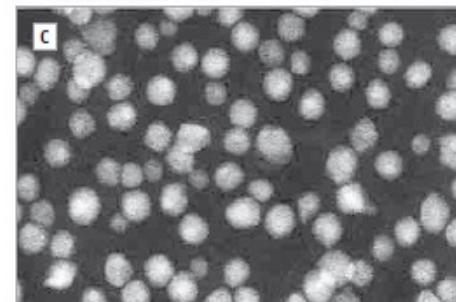
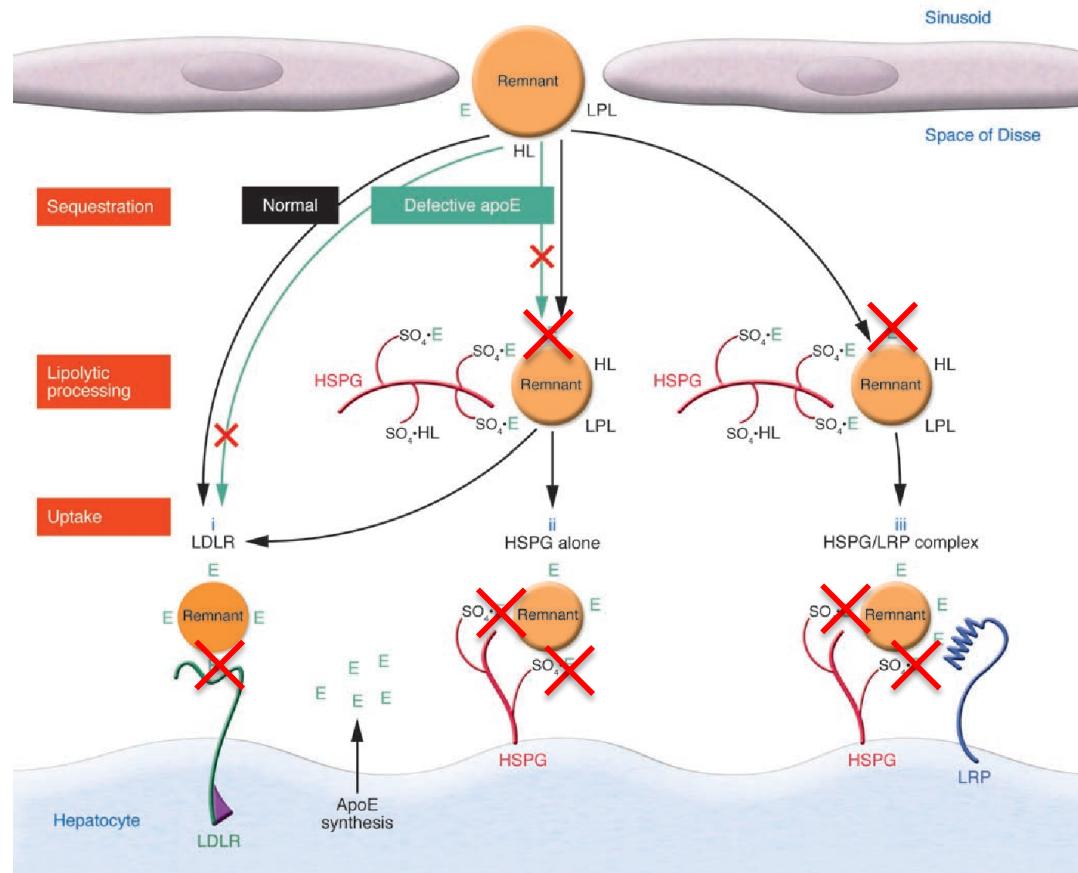
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### 3. Consequences on lipids/lipoprotein metabolism

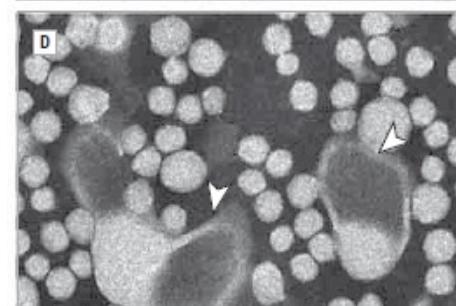


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### 3. Consequences on lipids/lipoprotein metabolism

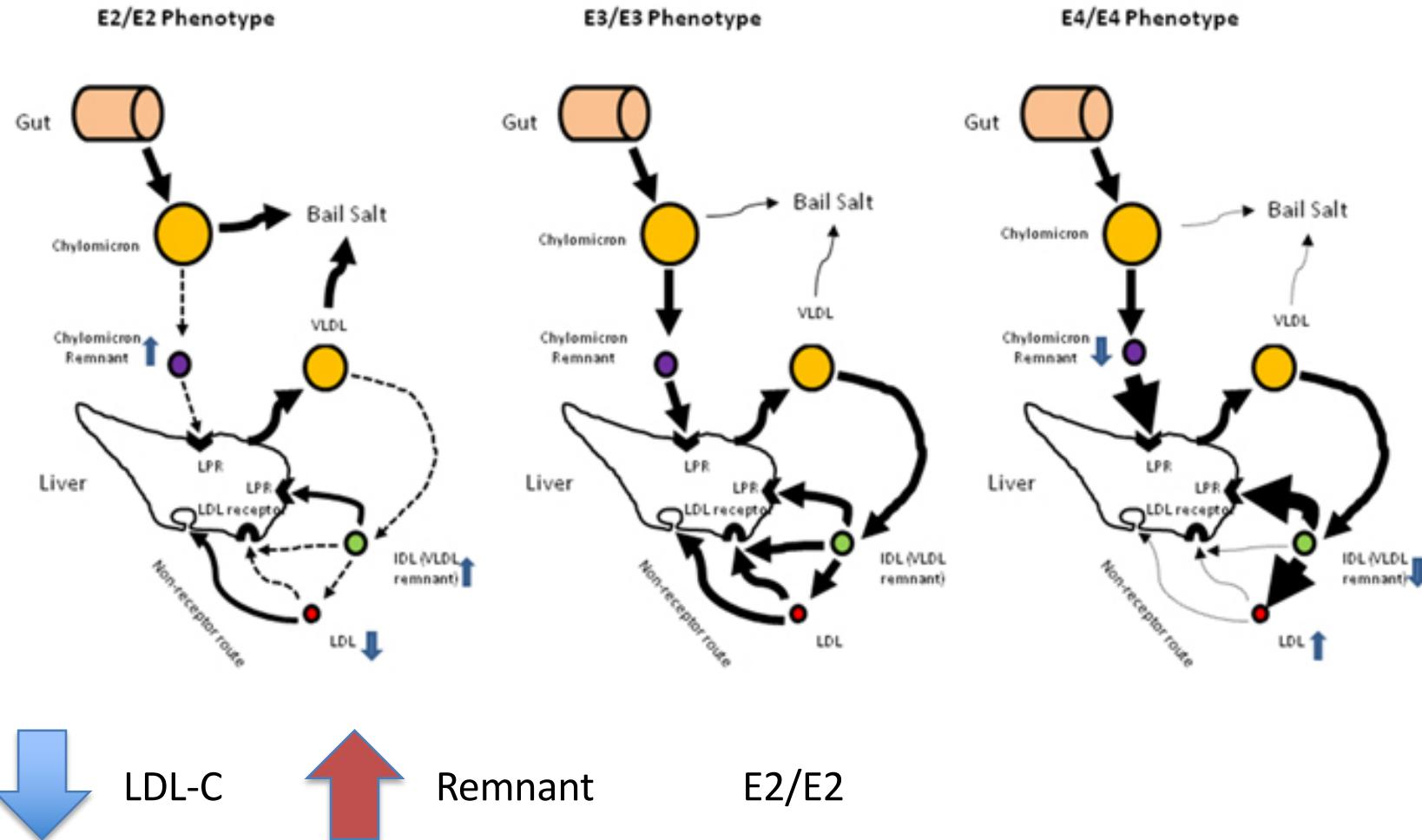


Control  
IDL



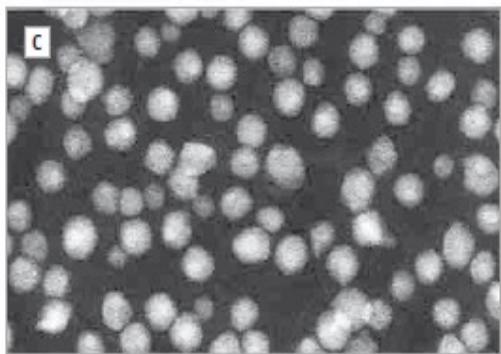
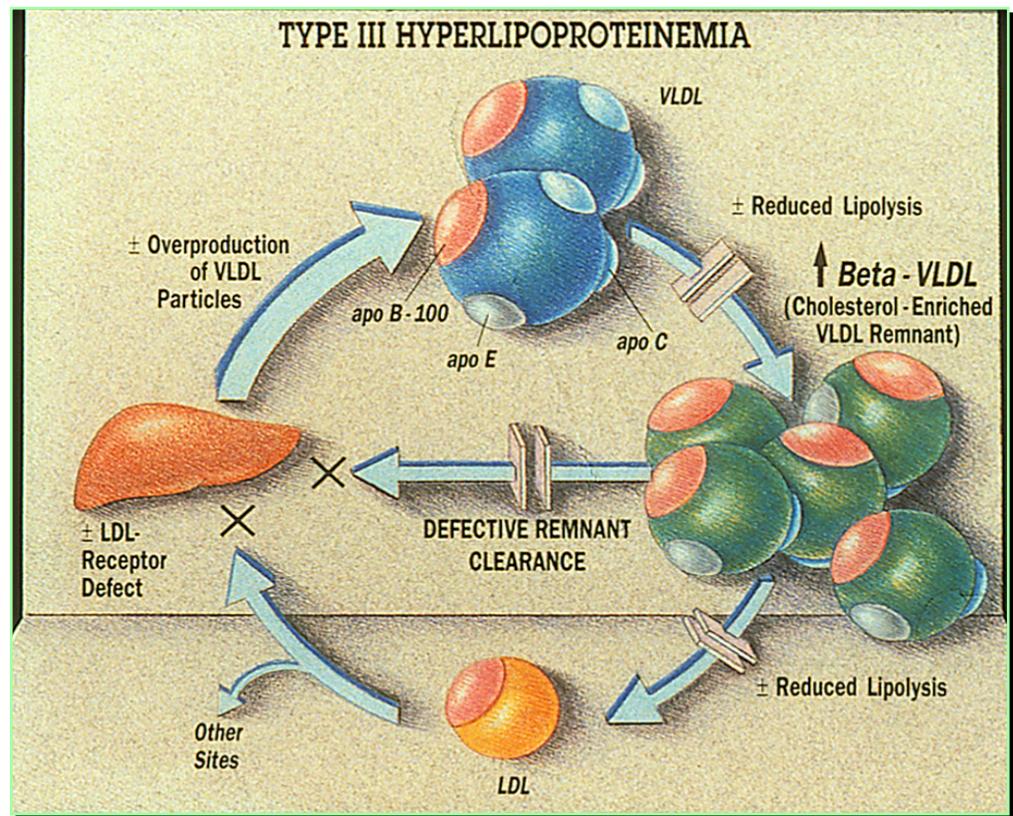
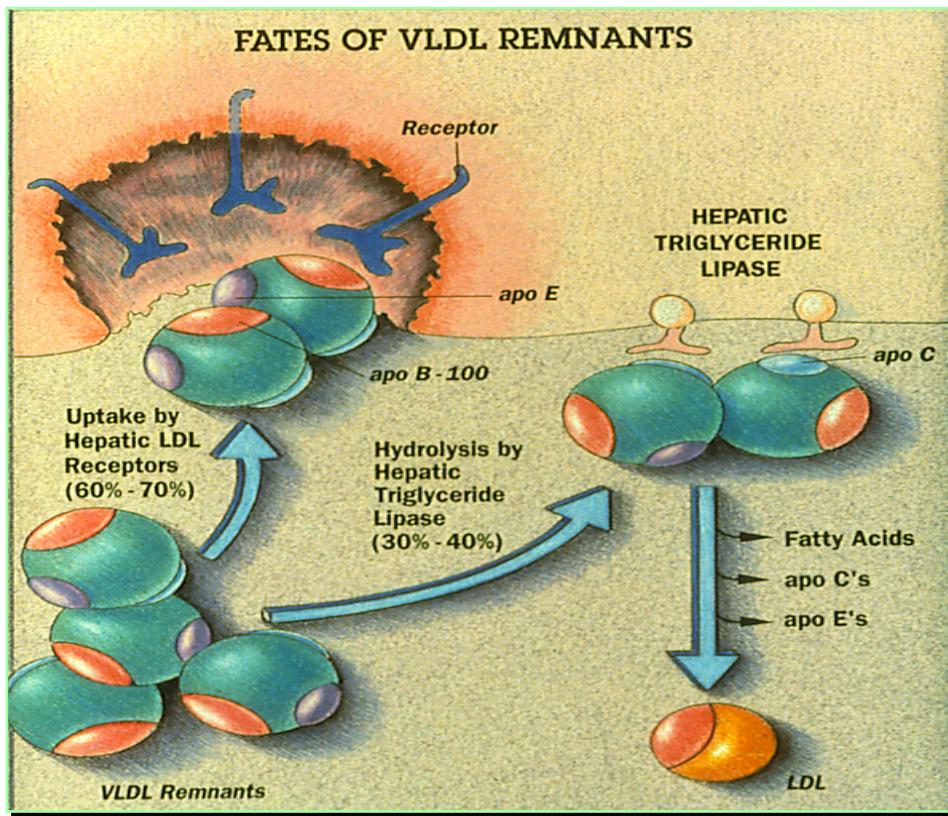
Proband  
IDL

### 3. Consequences on lipids/lipoprotein metabolism

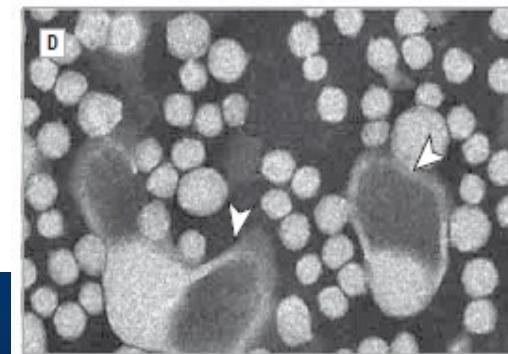


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### 3. Consequences on lipids/lipoprotein metabolism



Atherogenicity?



# Take home message I

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Type III hyperlipidemia is characterized by the disruption of remant cleareance in the liver



# DYSBETALIPOPROTEINAEMIA

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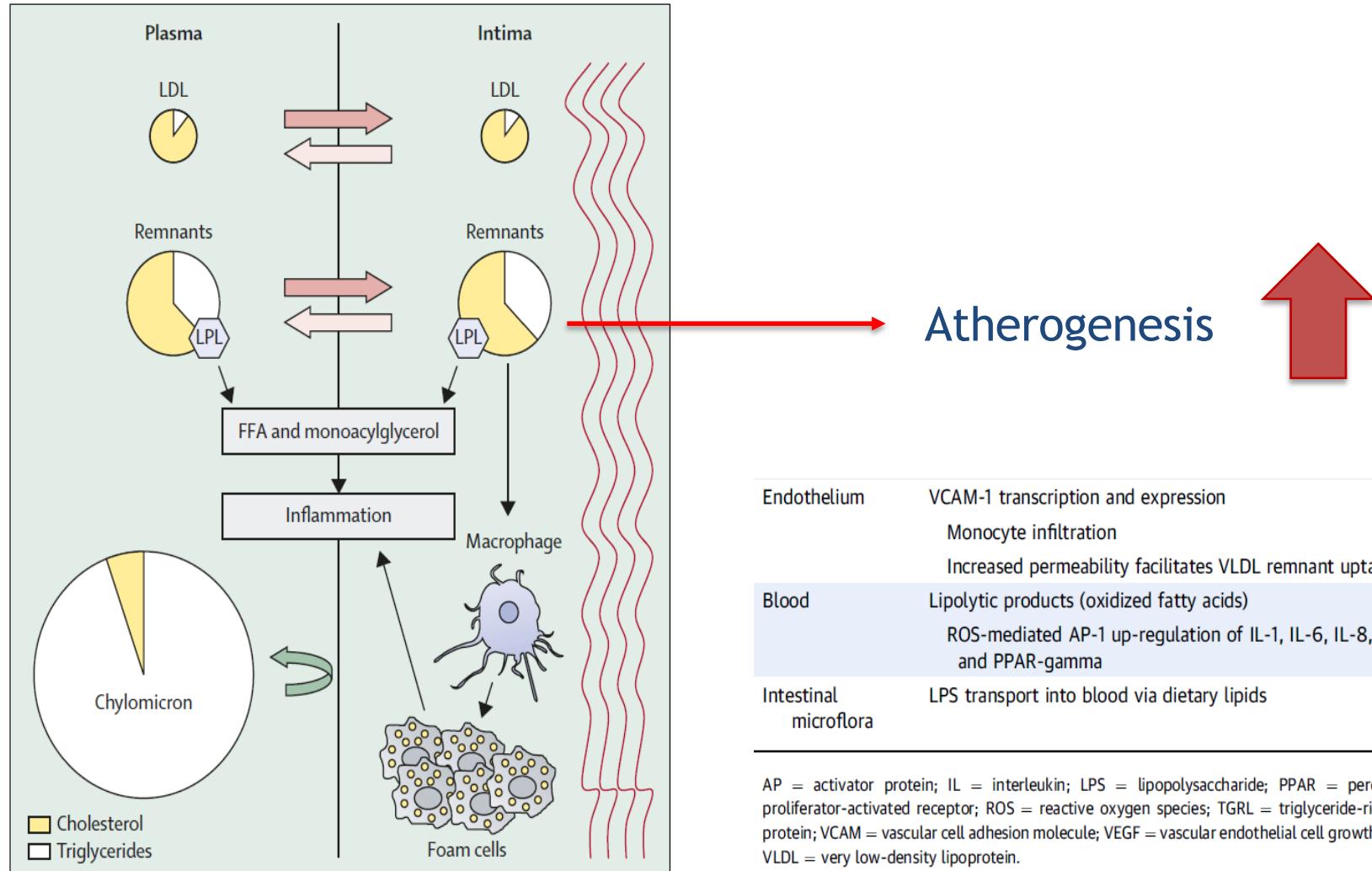
4. Remnant particles and atherosclerosis

5. Pharmacology



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## 4. Remnant lipoproteins and atherosclerosis

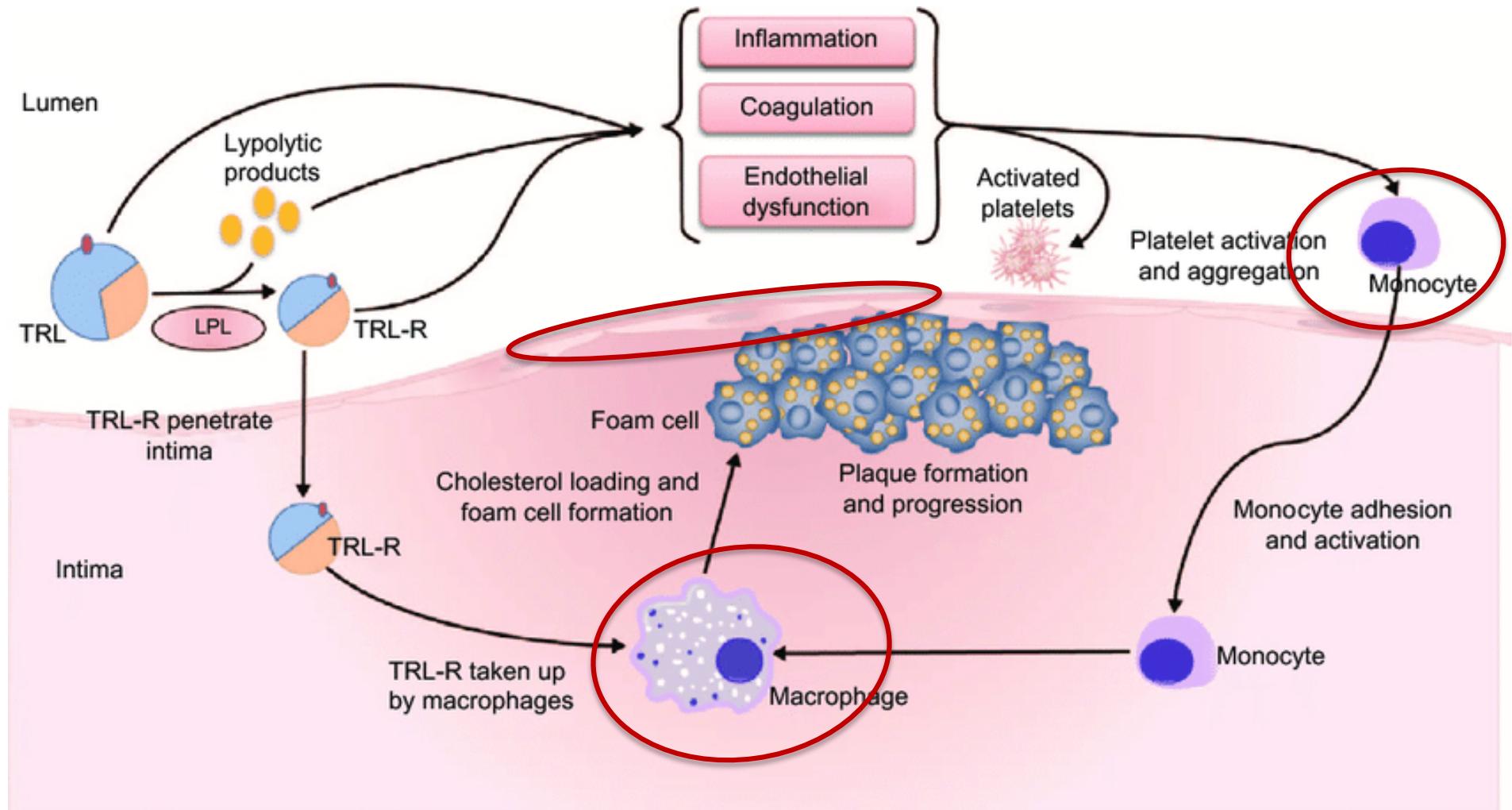


Nordestgaard and Varbo; Lancet 2014; 384: 626–635  
Rosensen et al. J Am Coll Cardiol 2014;64:2525–40.



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## 4. Remnant lipoproteins and atherosclerosis



# 4. Remnant lipoproteins and atherosclerosis

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<http://dx.doi.org/10.1016/j.jacc.2012.08.1026>

**Cardiometabolic Risk**

## **Remnant Cholesterol as a Causal Risk Factor for Ischemic Heart Disease**

Anette Varbo, MD,<sup>\*†‡</sup> Marianne Benn, MD, PHD, DMSc,<sup>\*†‡</sup>

Anne Tybjærg-Hansen, MD, DMSc,<sup>†‡§||</sup> Anders B. Jørgensen, MD,<sup>†‡§</sup>

Ruth Frikke-Schmidt, MD, PHD, DMSc,<sup>†‡§</sup> Børge G. Nordestgaard, MD, DMSc<sup>\*†‡§</sup>

*Herlev and Copenhagen, Denmark*



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## 5. Pharmacology

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-Dietary advice

Low cholesterol - low fat - low glycemic diet

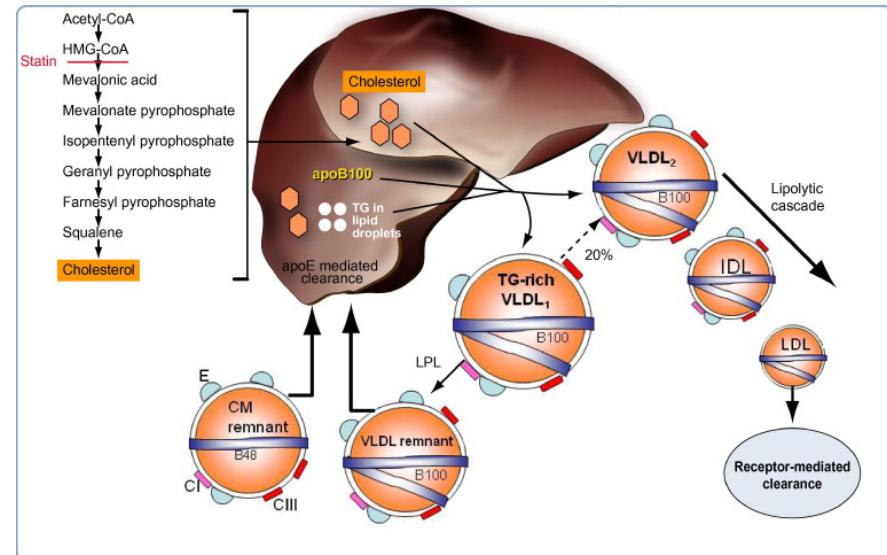


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# 5. Pharmacology

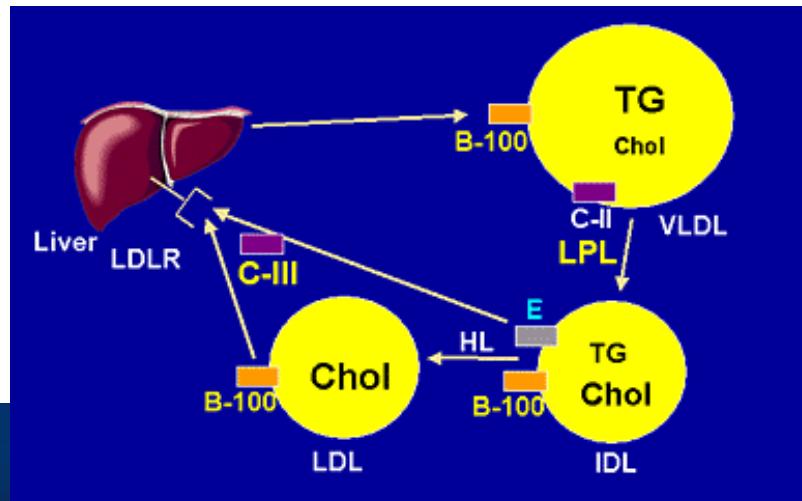
## ● Statins

(Increase LDL-R and increase apoE dependent uptake of remnants)



## ● Fibrates

(Increase lipolysis of TG in TGRL via LPL induction)



## 5. Pharmacology

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- **Statins**

(Increase LDL-R, increase apoE dependent uptake of remnants)

- **Fibrates**

(Increase lipolysis of TG in TGRL via LPL induction)

- **If needed, combination therapy**

- **Estrogen therapy may help some postmenopausal women with Type III Hyperlipidemia.**



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**Thanks**



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