

# FONDAZIONE S.I.S.A.

Per la promozione della ricerca sulle malattie da arteriosclerosi



**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**

**EAS**



This meeting is endorsed by the European Atherosclerosis Society

## **Familial Hypocholesterolemias (FHBL1, FHBL2, Abetalipoproteinemia, PCSK9 LOF, Chylomicron Retention Disease)**

**Marcello Arca**

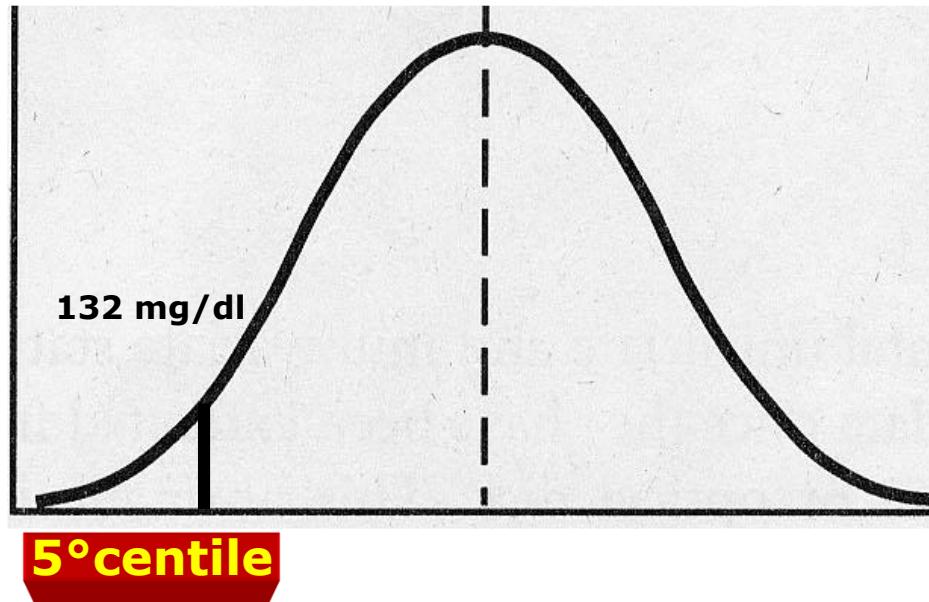
**Dipartimento di Scienze Cliniche e  
Specialità Mediche  
di Roma**



**SAPIENZA  
UNIVERSITÀ DI ROMA**

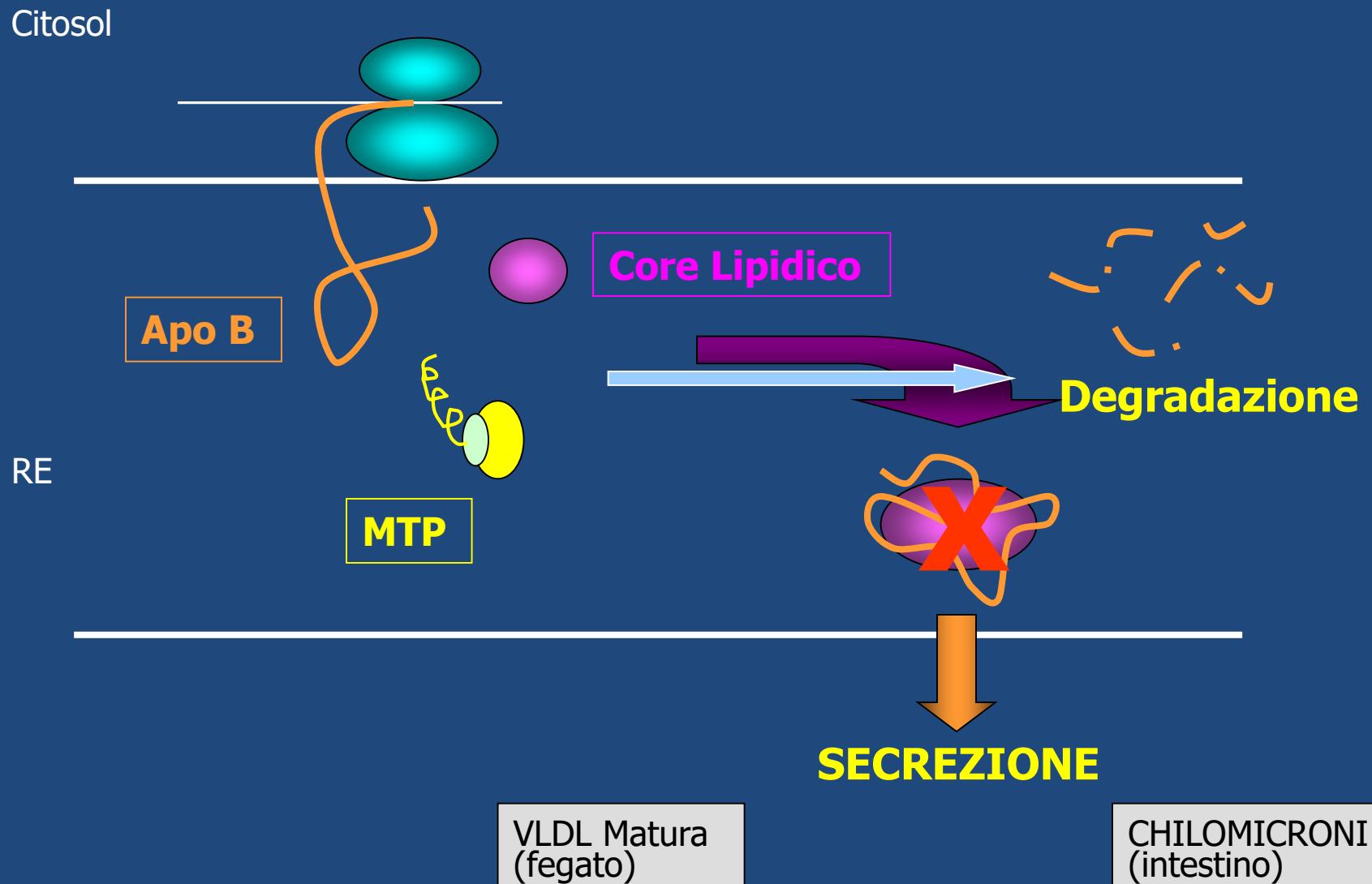
# Le ipocolesterolemie: definizione

**Sono definite da valori plasmatici di colesterolo totale, LDL colesterolo ed apoB inferiori al 5° percentile**



È possibile distinguere forme secondarie e forme primitive  
Le forme secondarie sono la conseguenza di altre patologie  
Le forme primitive sono trasmesse geneticamente e quindi presenti alla nascita

# ASSEMBLAGGIO DELLE LIPOPROTEINE CONTENENTI Apo B



# Ipocolesterolemie monogeniche

## ***Trasmissione autosomica co-dominante***

Ipobetalipoproteinemia Familiare (FHBL)

- Difetti del gene dell'APOB [Cr 2]
- PCSK9 [Cr 1]
- Altri geni

## ***Altre forme***

Ipolipidemia familiare combinata

- ❖ Difetti del gene ANGPTL3

## ***Trasmissione autosomica recessiva***

**ABETALIPOPROTEINEMIA (ABL)**

- ❖ Difetti del gene MTP [cr 4q22]

**CHYLOMICRON RETENTION DISEASE (CRD)**

- ❖ Difetti del gene SaralB (cr 5q31.1)

**Smith-Lemli-Opitz syndrome (SLOS)**

- ❖ Difetti del gene DHCR7

# Difetto di Assemblaggio delle Lipoproteine contenenti ApoB

## *Abetalipoproteinemia (ABL)*

Rara: trasmissione autosomica recessiva

Mutazioni nel gene della MTP

Frequenza non nota: 50 casi descritti in letteratura

LDL-C: non rilevabile

Apo B: non rilevabile

Enterociti infarciti di grassi

Acantocitosi; sequele neurologiche da deficit di vitamina E; retinite pigmentosa

# Livelli Lipidici e Apoproteici Plasmatici in due Famiglie con Abetalipoproteinemia

Subject	Age (years)	TC (mg/dl)	TG (mg/dl)	LDL-C (mg/dl)	HDL-C (mg/dl)	Apo B (mg/dl)	Apo A-I (mg/dl)
Proband	3	48	11	nd	45	nd	71
Mother	32	186	245	88	49	77	177
Father	32	219	203	149	29	94	118

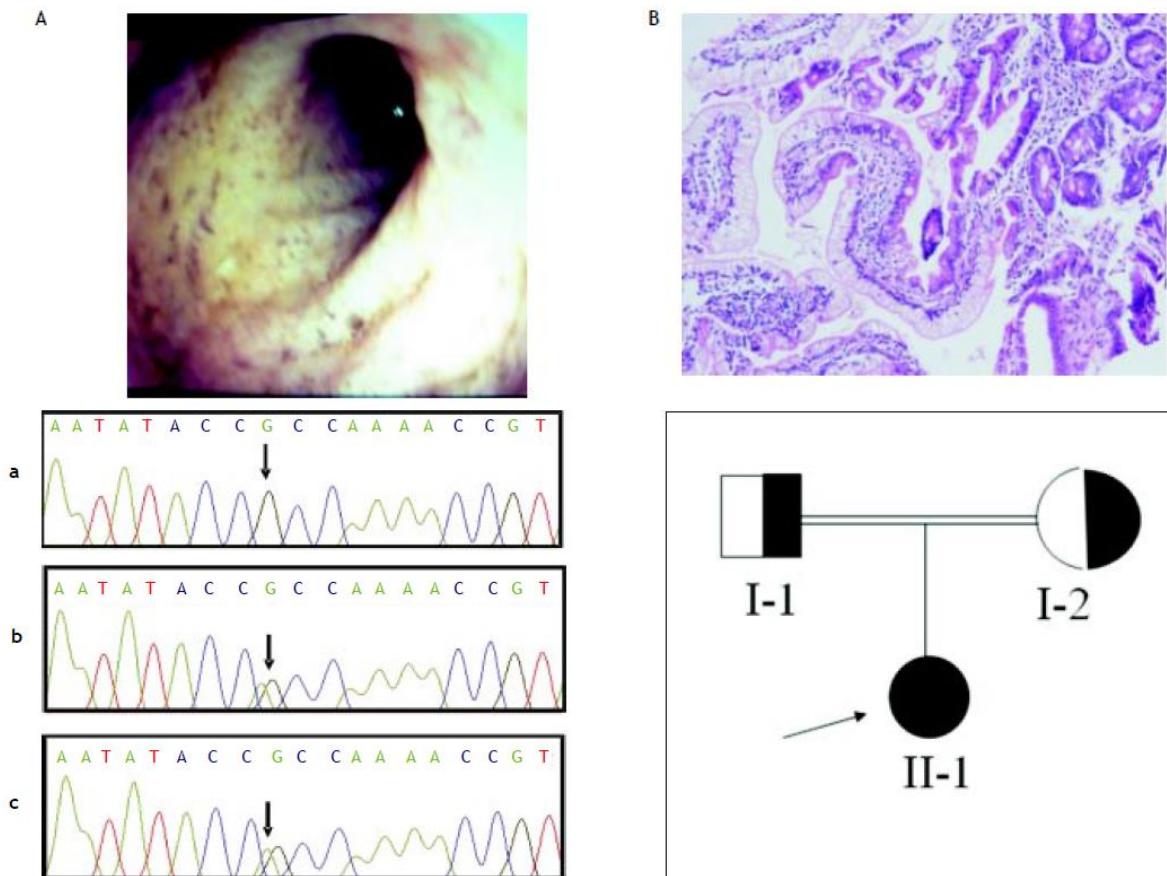
  

Subject	Age (years)	TC (mg/dl)	TG (mg/dl)	LDL-C (mg/dl)	HDL-C (mg/dl)	Apo B (mg/dl)	Apo A-I (mg/dl)
Proband	39	24	11	nd	19	nd	41
Mother	69	268	78	188	69	127	186
Father	69	264	133	203	31	152	106

# Identification of a novel mutation of *MTP* gene in a patient with abetalipoproteinemia

Mehri Najafi Sani,\* Mozhgan Sabbaghian,<sup>†</sup>  
Fatemeh Mahjoob,<sup>†</sup> Angelo B. Cefalù,<sup>‡</sup> Maurizio R. Averna,<sup>‡</sup> Nima Rezaei<sup>§,||</sup>

Cholesterol	22 mg/dL
Triglyceride (TG)	13 mg/dL
Low density lipoprotein (LDL)	12 mg/dL
High density lipoprotein (HDL)	15 mg/dL
Very low density lipoprotein (VLDL)	3 mg/dL



# Difetti della Secrezione dei Chilomicroni

## ***Malattia di Anderson o Chylomicron Retention Disease (CRD)***

Rara: trasmissione autosomica recessiva

Mutazioni nel gene della SAR1b

Frequenza non nota: meno di 50 casi descritti in letteratura (solo 34 casi con diagnosi genetico-molecolare)

- Concentrazioni plasmatiche:

ApoB: ridotta 50 %-assenza di ApoB 48

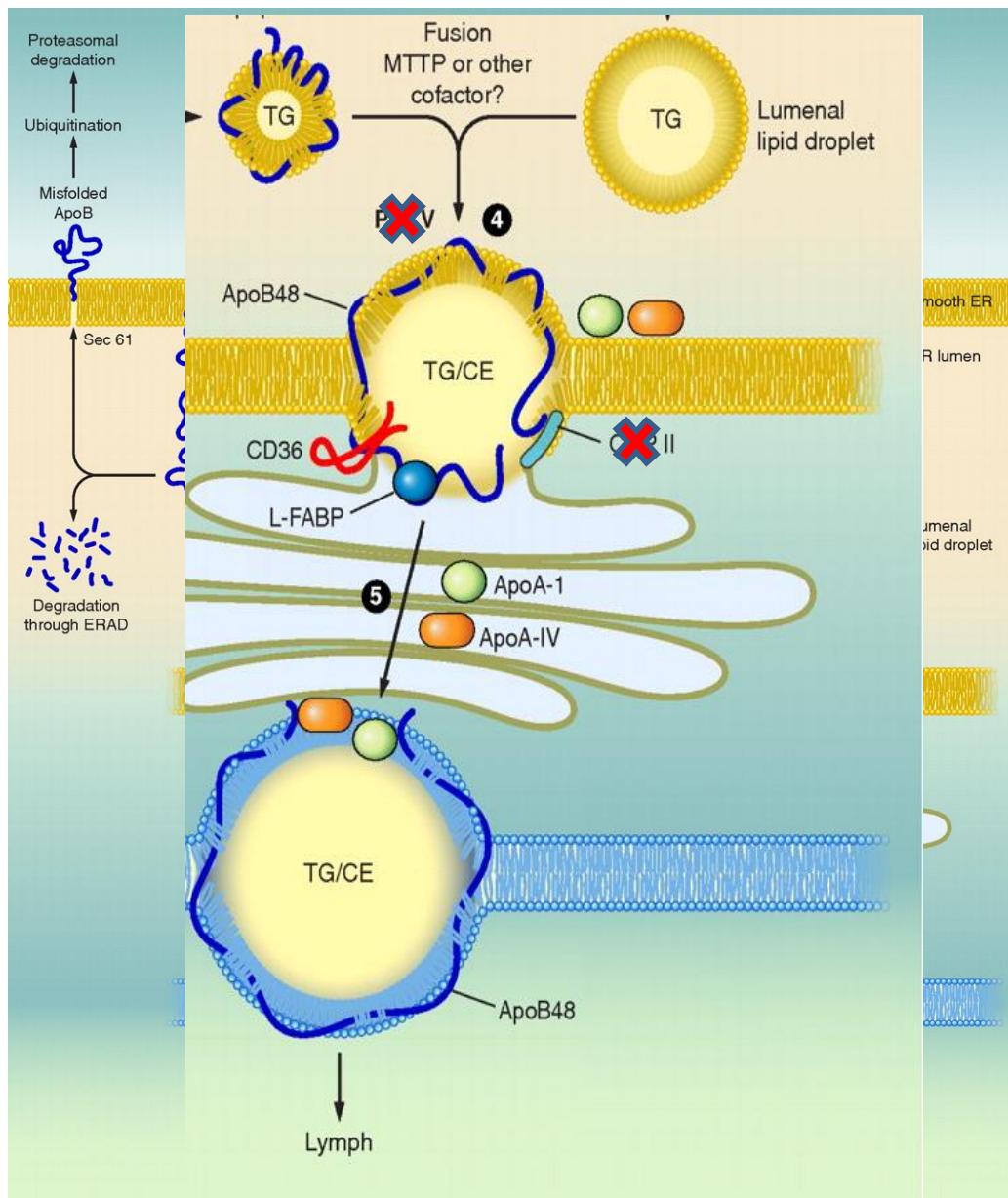
Chilomicroni: assenti

Trigliceridi: normali

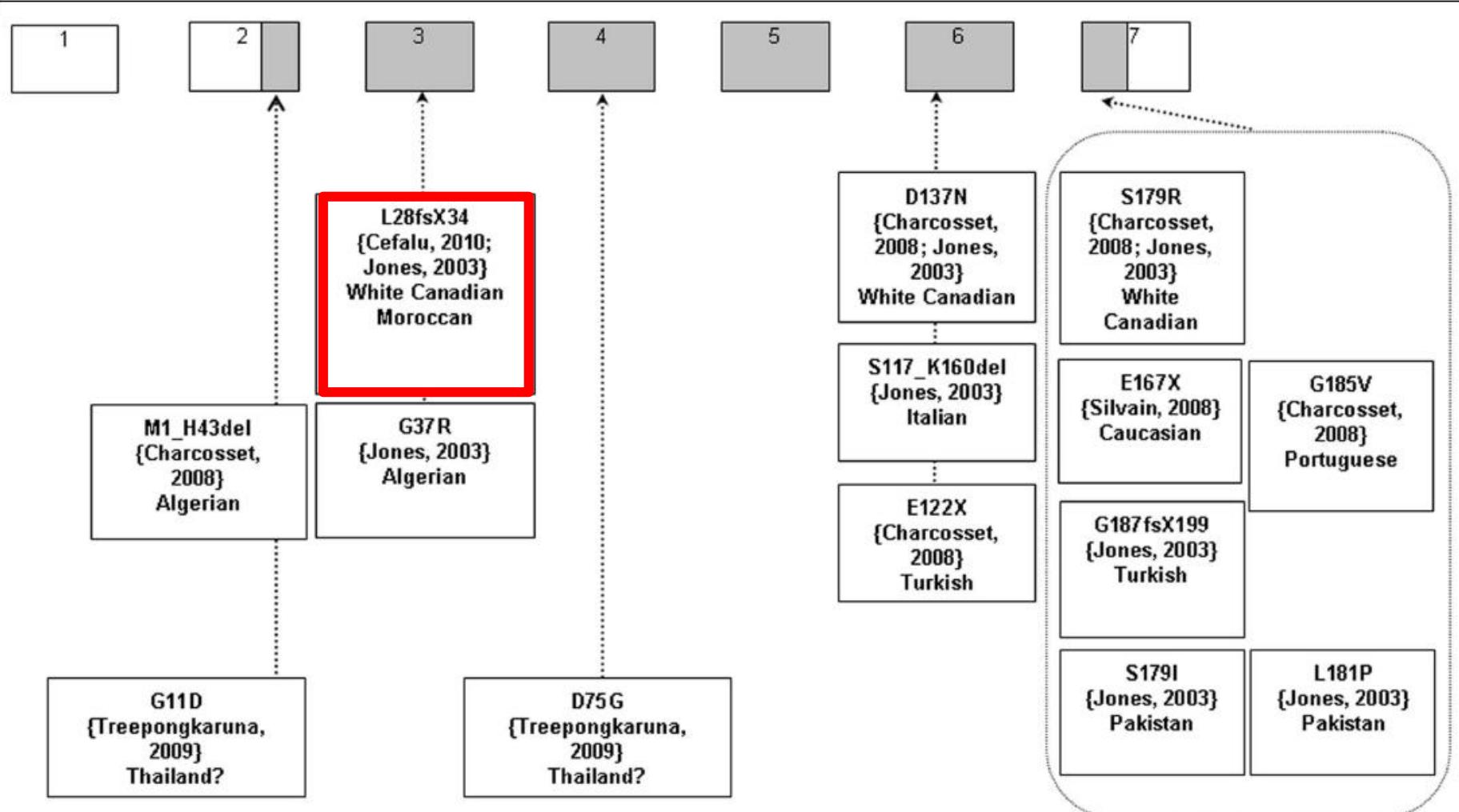
- Assorbimento lipidico: *malassorbimento con steatorrea*  
*Enterociti infarciti di grassi*

- Clinica: *acantocitosi; perdita dei riflessi osteo-tendinei; assenza di retinite pigmentosa; bassi livelli di Vit. E; ritardo di crescita*

# Model of intestinal triglyceride-rich lipoprotein assembly.



# MUTAZIONI DEL GENE SARA1B IN PAZIENTI CON CRD DESCRITTE IN LETTERATURA



# Diagnosi di CRD

## Clinical

<b>Anthropometry</b>	Constant but unspecific failure to thrive in early infancy (1-6 months)
<b>Digestive</b>	Chronic malabsorptive diarrhea in early infancy, frequent vomiting and abdominal distension in early infancy
<b>Neurology</b>	Areflexia, ↓ deep proprioception, and ataxia are uncommon during childhood and there is no retinopathy
	<b>Biological</b> (Fasting State)
<b>Lipids</b>	In patients with a suggestive profile: ↓ HDL and N <sup>al</sup> TG are the most discriminative specificities of CRD. ↓↓ Total cholesterol and ↓↓ LDL: intensity of decrease only around 50% normal values
<b>Neuromuscular</b>	↑ (1.5-4N) CK discriminative but inconstant abnormalities for CRD
<b>Blood Cell Count</b>	Absence of acanthocytosis in infancy is more frequent in CRD than in AB or HB
<b>Hepatic</b>	Frequent and early but not specific ↑ (1.5-3N) AST and/or ALT, with normal GGT, bilirubin and alkaline phosphatase
<b>Liposoluble vitamins</b>	Unspecific decrease ↓↓ E is the most severe and only permanent vitamin deficiency even with supplementation, ↓↓ A, ↓ - N <sup>al</sup> D, ↓ - N <sup>al</sup> K
<b>Coagulation</b>	↓ - N <sup>al</sup> INR. Decreased INR if there is vitamin K deficiency
<b>Plasma fatty acid</b>	Abnormal profile, omega 6 linoleic acid deficiency, normal omega 3
<b>Fasting lipids in parents</b>	N <sup>al</sup>

## Upper Endoscopy (fasting state or after enriched fat diet for 3 days)

Unspecific white duodenal mucosa

Optic microscopy      Villi are normal but the enterocytes are grossly distended by lipid droplets

Electron microscopy      Chylomicron-like aggregates, membrane bound?

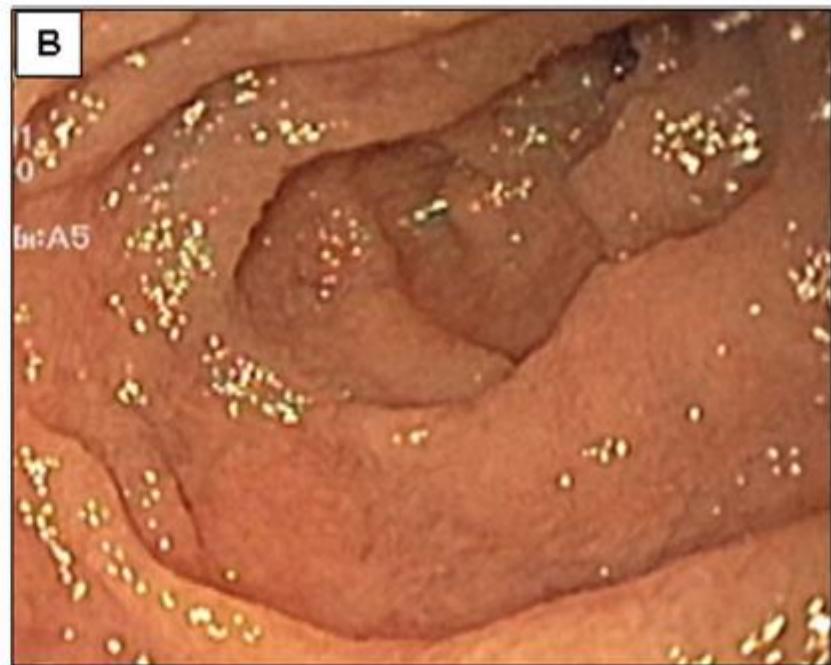
## Genotyping

Mutations in SAR1B, Chromosome 5

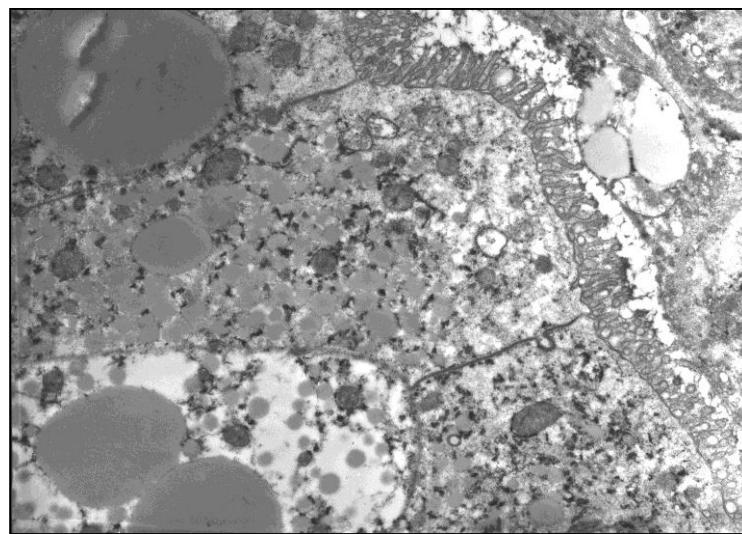
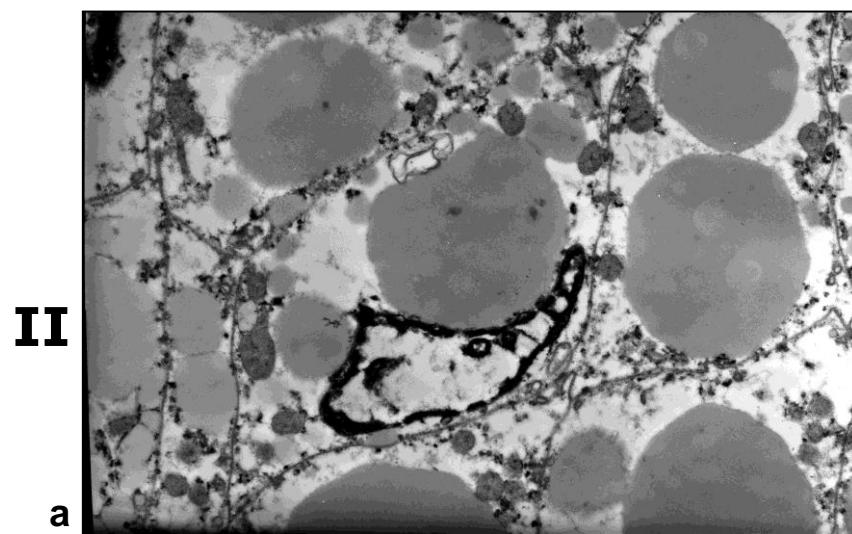
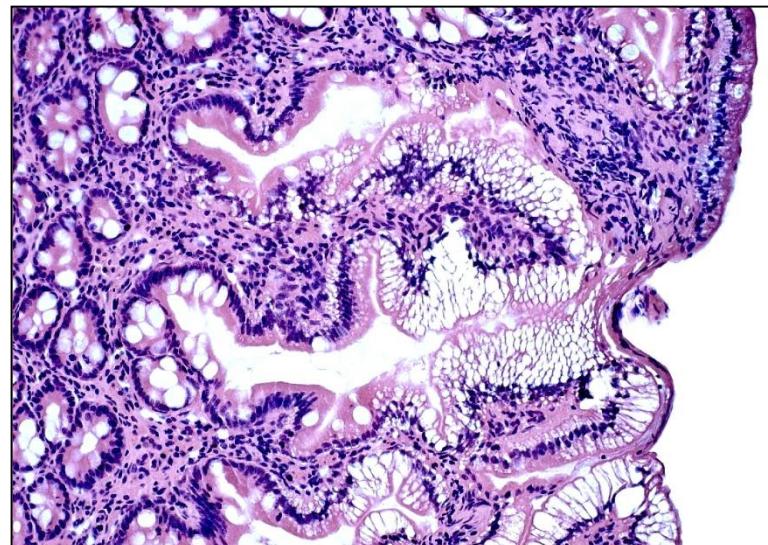
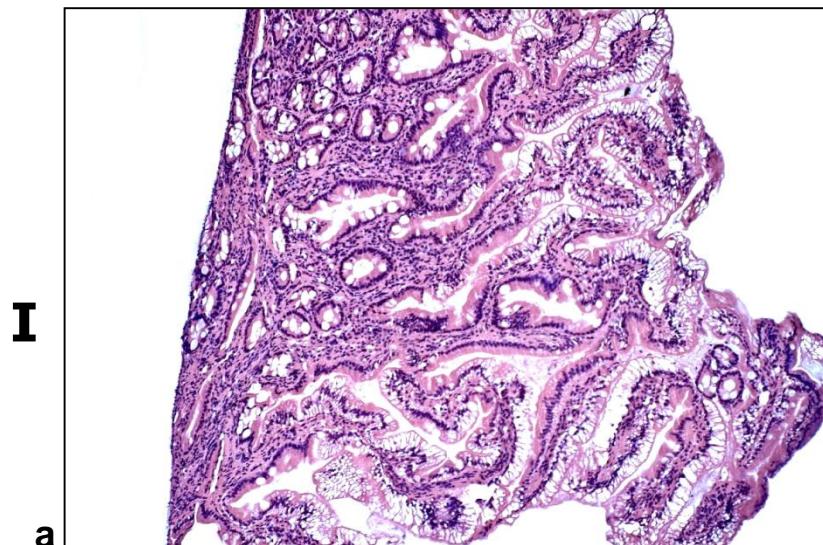
## Summary

- 1) Chronic diarrhea in young infants (< 6 Mo). Normal TG with decreased total cholesterol, LDL-C and HDL-C
- 2) Failure to thrive
- 3) White duodenal mucosa at endoscopy → genetic hypcholesterolemia?
- 4) Genetic mutation of SAR1B → CRD confirmed

# Aspetto endoscopico della mucosa duodenale



# Biopsia Intestinale



# Trattamento della CRD e della Abetalipoproteinemia

Early diagnosis without neurological complications: PO

Delayed diagnosis and neurological complications: PO + IV

## Diet

Low-fat diet

Enriched in essential fatty acids (vegetable oils, fish...)

± Enriched in medium-chain triglycerides

## Liposoluble Vitamins PO

Vitamin E (hydrosoluble form): 50 IU/kg/d

Vitamin A: 15,000 IU/d (adjust according to plasma levels)

Vitamin D: 800-1200 IU/kg/d or 100,000 IU/2 month if < 5 y old, and 600,000 IU/2 month if > 5 y old

Vitamin K: 15 mg/week (adjust according to INR and plasma levels)

## One perfusion/month

Fatty acids: intralipid 20% 2 g/kg/month

Vitamin E: 4 to 6 mg/kg/month

Vitamin A: 500 IU/kg/month

# FHBL

Malattia genetica a trasmissione autosomica co-dominante caratterizzata da bassi livelli plasmatici di colesterolo, totale ed LDL, ed apolipoproteina B (<5°percentile)

-128, 70 e 50 mg/dl-

- La forma **eterozigote** è solitamente asintomatica anche se è stata documentata la presenza di steatosi epatica
- La forma **omozigote** può essere asintomatica ma nella maggior parte dei casi è caratterizzata da malassorbimento dei grassi, retinite pigmentosa, neuropatia e steatosi epatica

# Il Fenotipo FHBL

## Mutazioni del gene apoB

- 44 mutazioni nonsenso responsabili della sintesi di varie forme troncate di apoB "visibili" o "non visibili" nel plasma;
- 1 mutazione missenso
  - Difetti di altri geni

3p21 e 13q

# Prevalenza di apo B troncate nello Studio Siciliano della Ipocoolesterolemia Primitiva

7000 donatori

TC < 128 mg/dl: 7.1 %

Frequenza Apo B troncate tra gli ipocoolesterolemici: 1.0 %

Frequenza apo B troncate nella popolazione generale: 0.08 %

# Normale

fegato

mRNA

intestino

mRNA

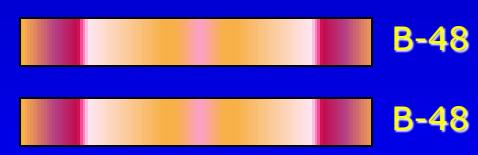


# Ipobetalipoproteinemia

fegato

intestino

*stop codon >48% Apo B*



*stop codon <48% Apo B*



# *Le FAQ della FHBL*

- *Perché i livelli di Colesterolo ed Apo B sono ridotti?*
- *Perché la sintomatologia intestinale è assente?*
- *I soggetti FHBL sono protetti dalle MCV?*
- *La FHBL è geneticamente eterogenea?*
- *Perché c'è steatosi epatica?*

# Apoprotein B-100 Production Is Decreased in Subjects Heterozygous for Truncations of Apoprotein B

# *Schonfeld, Gustav et Al* ATVB 1995

## B89, B75, B54.8, B52, B31

	Production rate	FCR
• VLDL-ApoB	36%	≈
• LDL-ApoB	29%	≈

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# Postprandial lipemia in subjects with hypobetalipoproteinemia and a single intestinal allele for apoB-48.

Averna M, Seip RL, Mankowitz K, Schonfeld G.

JLR1993

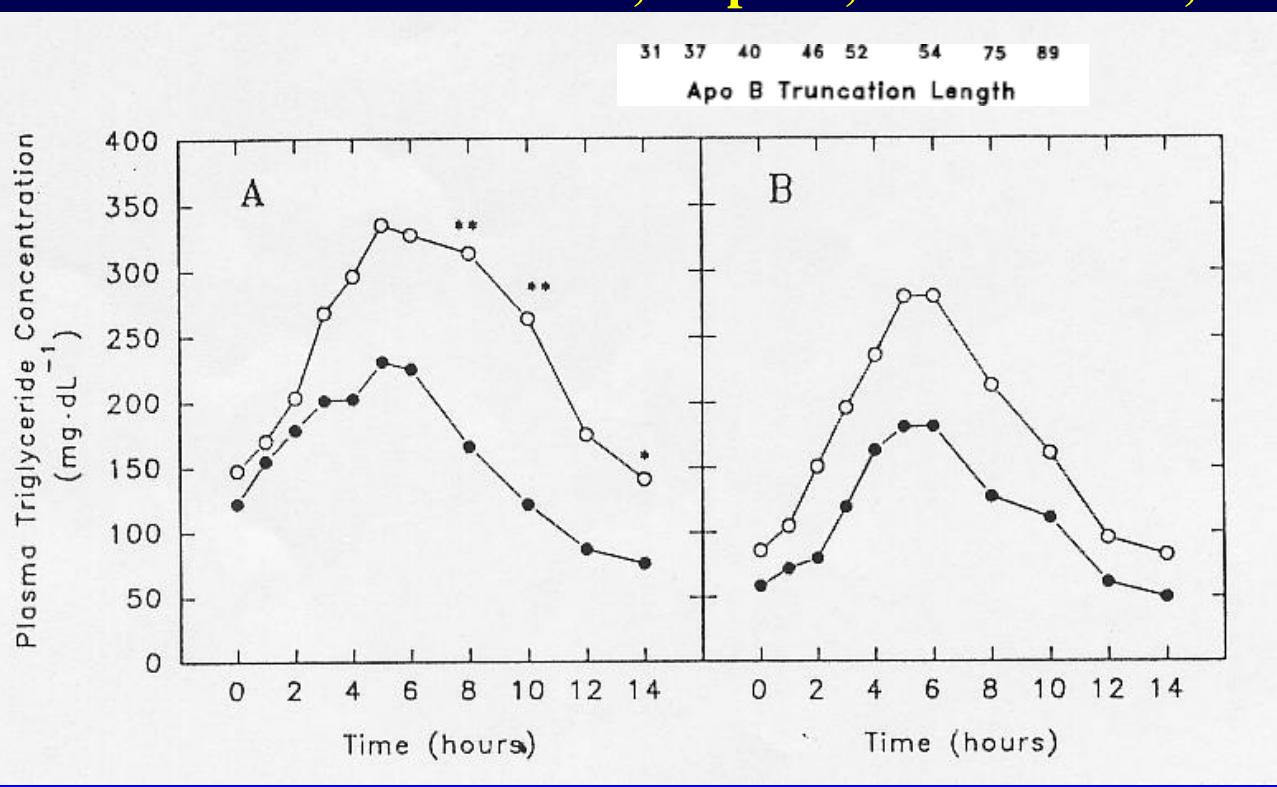


TABLE 7. Vitamin A and E plasma levels in hypobetalipoproteinemic subjects and in controls

Subjects	Chol	LDL-C	TG	Vit. A	Vit. E	Vit. E/Chol	Vit. E/LDL-Chol
Controls (44)	204 ± 40	128 ± 40	125 ± 53	65 ± 33	1162 ± 441	5.8 ± 2.2	9.9 ± 4.8
Hypobeta B > 48 (7)	123 ± 20*	52 ± 21*	88 ± 74	79 ± 24	536 ± 198*	4.4 ± 1.4	11.4 ± 4.4
B < 48 (7)	102 ± 36*	38 ± 26*	60 ± 25*	64 ± 29	372 ± 155*	3.5 ± 9*	12.1 ± 7.8

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# Amino Terminal 38.9% of Apolipoprotein B-100 Is Sufficient to Support Cholesterol-Rich Lipoprotein Production and Atherosclerosis

*Schonfeld, Gustav et Al*

*ATVB 2003*

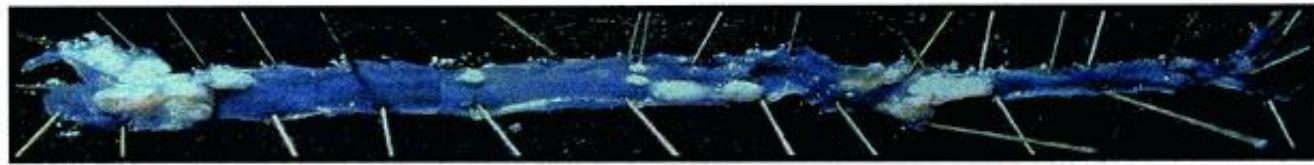
***Apob<sup>+/+</sup>/Apoe<sup>+/+</sup>***



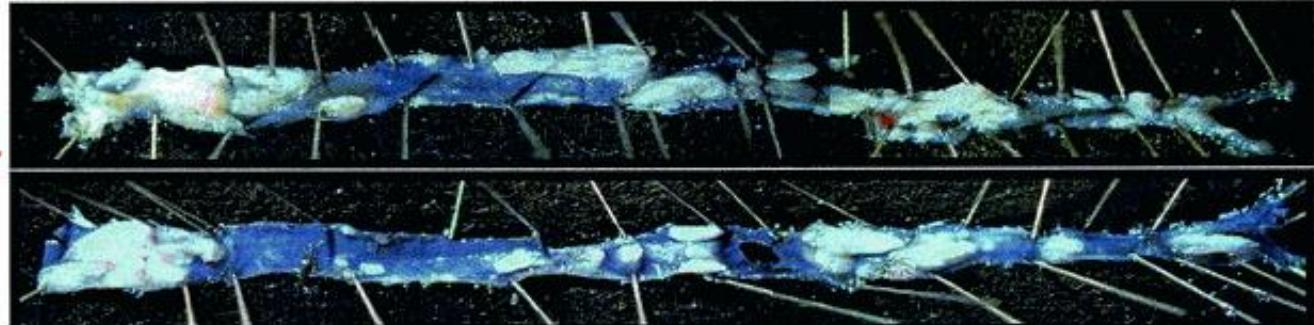
***Apob<sup>+/+</sup>/Apoe<sup>-/-</sup>***

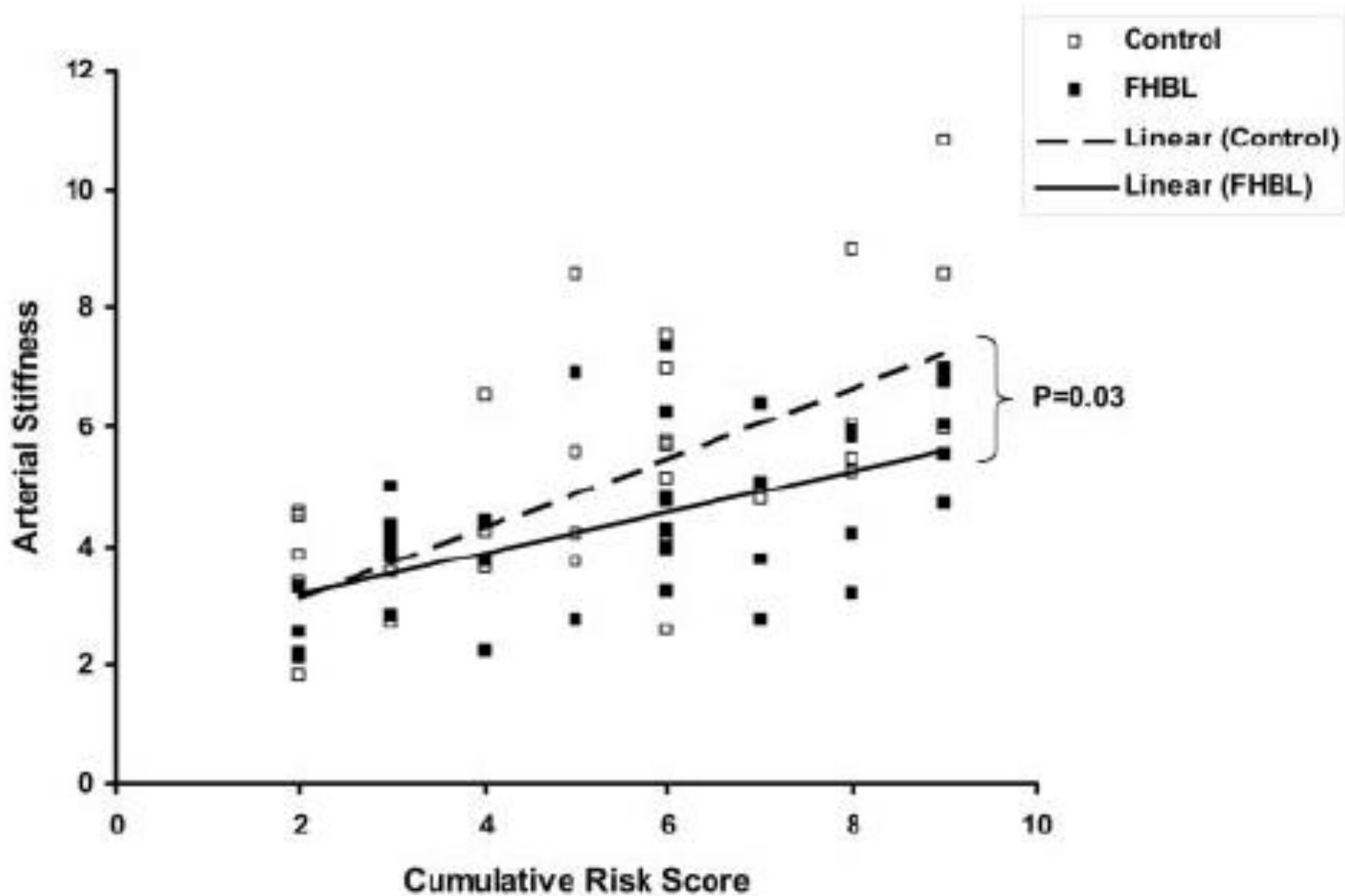


***Apob<sup>38.9/+</sup>/Apoe<sup>-/-</sup>***



***Apob<sup>38.9/38.9</sup>/Apoe<sup>-/-</sup>***

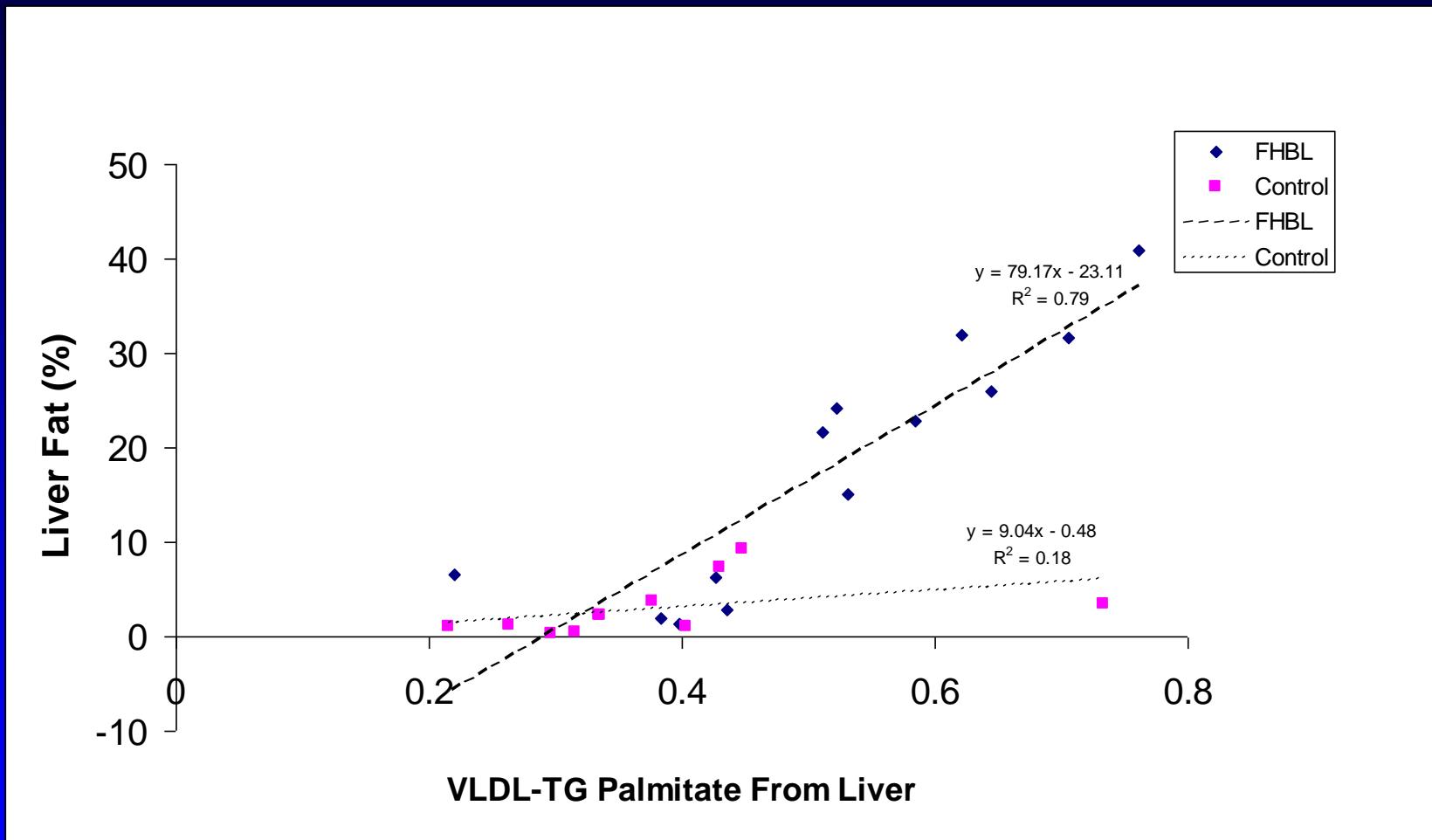




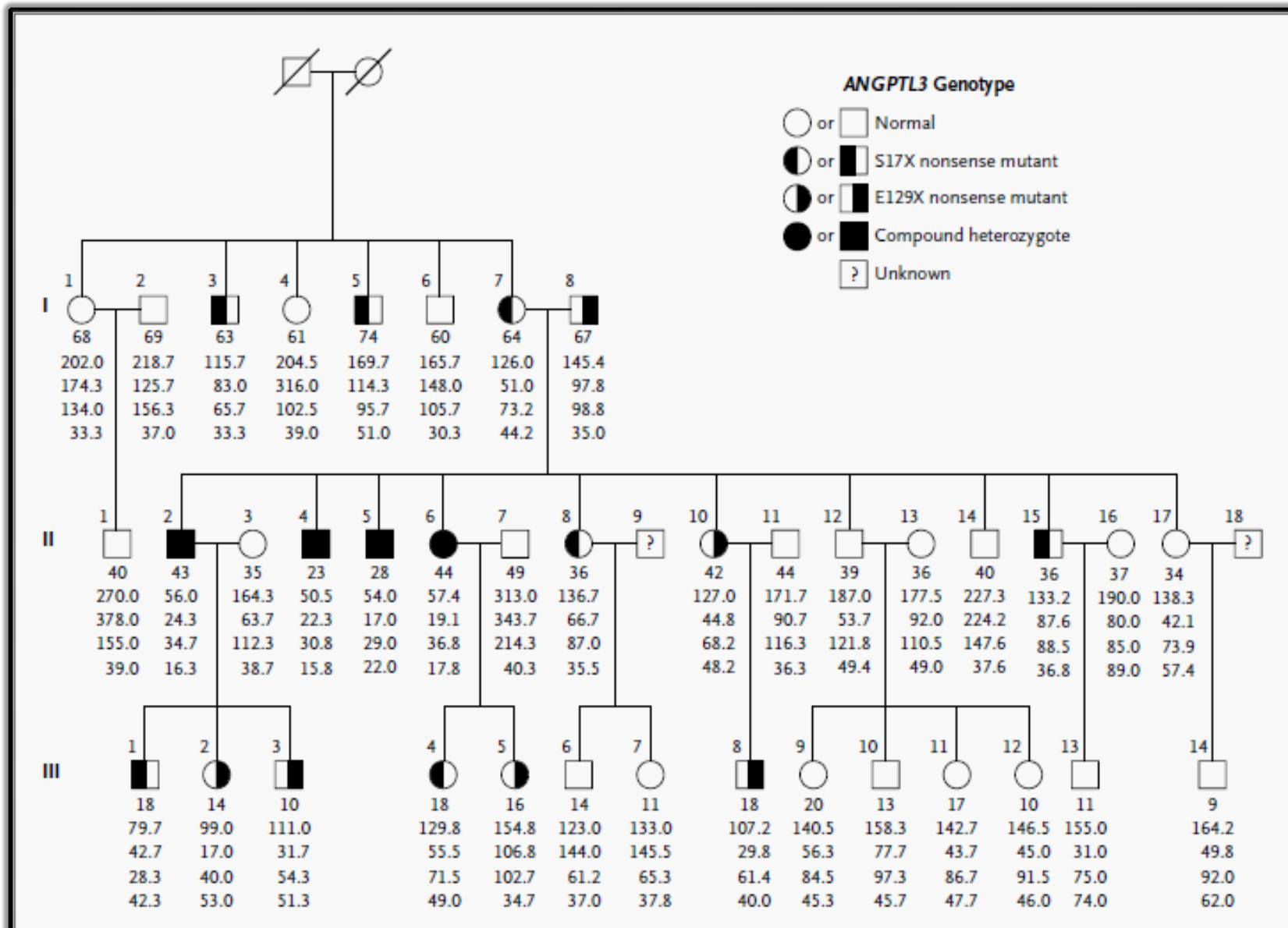
# *Le FAQ della FHBL*

- *Perché i livelli di Colesterolo ed Apo B sono ridotti?*
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# Fatty Liver in Familial Hypobetalipoproteinemia: Triglycerides Assembly into VLDL Particles is Affected by the Extent of Hepatic Steatosis



# Pedigree of the Study Family with Familial Combined Hypolipidemia



# *Journal of patient-oriented and epidemiological research*

## Clinical characteristics and plasma lipids in subjects with familial combined hypolipidemia: a pooled analysis<sup>§</sup>

Ilenia Minicocci,<sup>\*</sup> Sara Santini,<sup>\*</sup> Vito Cantisani,<sup>†</sup> Nathan Stitziel,<sup>§</sup> Sekar Kathiresan,<sup>\*\*</sup> Juan Antonio Arroyo,<sup>††</sup> Gertrudis Martí,<sup>§§</sup> Livia Pisciotta,<sup>\*\*\*</sup> Davide Noto,<sup>†††</sup> Angelo B. Cefalù,<sup>†††</sup> Marianna Maranghi,<sup>\*</sup> Giancarlo Labbadia,<sup>\*</sup> Giovanni Pigna,<sup>\*</sup> Fabio Pannozzo,<sup>§§§</sup> Fabrizio Ceci,<sup>\*\*\*\*</sup> Ester Ciociola,<sup>\*</sup> Stefano Bertolini,<sup>\*\*\*</sup> Sebastiano Calandra,<sup>††††</sup> Patrizia Tarugi,<sup>§§§§</sup> Maurizio Averna,<sup>†††</sup> and Marcello Arca<sup>1,\*</sup>

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# Plasma lipoproteins in FHBL2 carriers and non-carriers controls identified within families and in the whole cohort.

Variables	Family study (n=225)			All subjects (n=517)			
	FHBL2 (n=98)		Non carriers (n=127)	FHBL2 (n=115)		Non carriers (n=402)	
	Homozygous / Compound	Heterozygous		Homozygous / Compound	Heterozygous		
			Homozygotes		Heterozygotes		
TC (mmol/L)							
LDL-C			- 67%		- 9%		
TG			- 71%		- 21%		
HDL-C			- 39%		- 17%		
LDL-C (mmol/L)							
ApoB			- 48%		- 7%		
	(n=19)	(n=79)	(n=127)	(n=22)	(n=93)	(n=402)	
ApoB (g/L)	0.5 ± 0.1 ***### (0.3 – 0.7) (n=19)	0.8 ± 0.2 (0.4 – 1.3) (n=79)	0.9 ± 0.2 (0.5 – 1.6) n=126	0.5 ± 0.1 ***### (0.3 – 0.7) n=20	0.8 ± 0.2 § § (0.3 – 1.3) n=92	0.9 ± 0.2 (0.5 – 1.8) n=398	
ApoAI (g/L)	0.7 ± 0.2 ***### (0.4 – 1.1) n=18	1.5 ± 0.3 (0.7 – 2.2) n=79	1.6 ± 0.3 (1.0 – 2.4) n=114	0.7 ± 0.2 ***### (0.4 – 1.1) n=18	1.5 ± 0.4 § (0.7 – 2.2) n=92	1.6 ± 0.3 (0.9 – 2.4) n=302	
Lp(a) (μmol/L)	0.2 (0.1 – 2.1) n=13	0.5 (0.2 – 0.9) n=70	0.6 (0.2 – 1.9) n=85	0.2 (0.2 – 1.2) n=13	0.5 (0.2 – 0.9) n=78	1.0 (0.1 – 2.1) n=193	

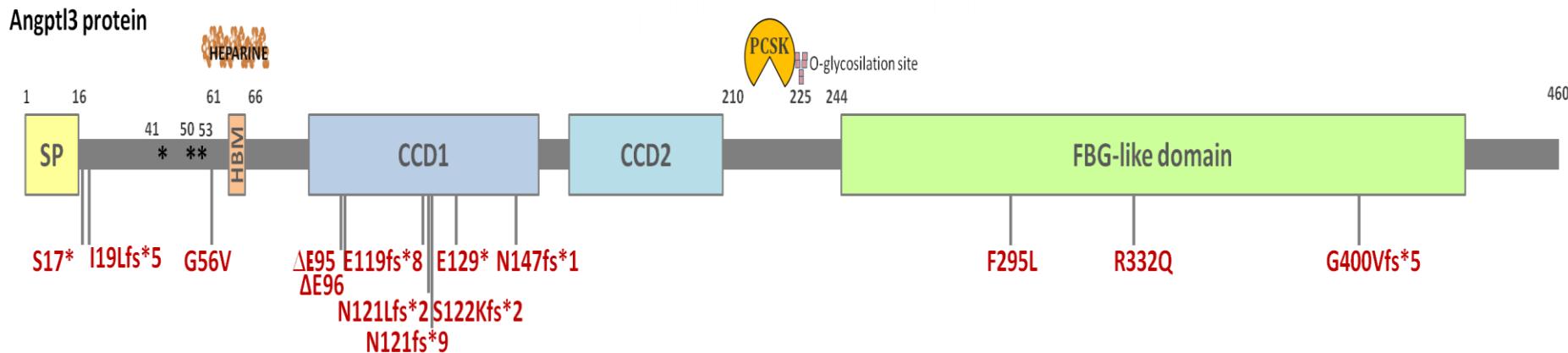
\*p<0.05 \*\*p≤0.01 \*\*\*p<0.001 for comparison between non-carriers vs homozygotes carriers.

§ p<0.05 §§ p<0.01 §§§ p<0.001 for comparison between non-carriers vs heterozygotes carriers.

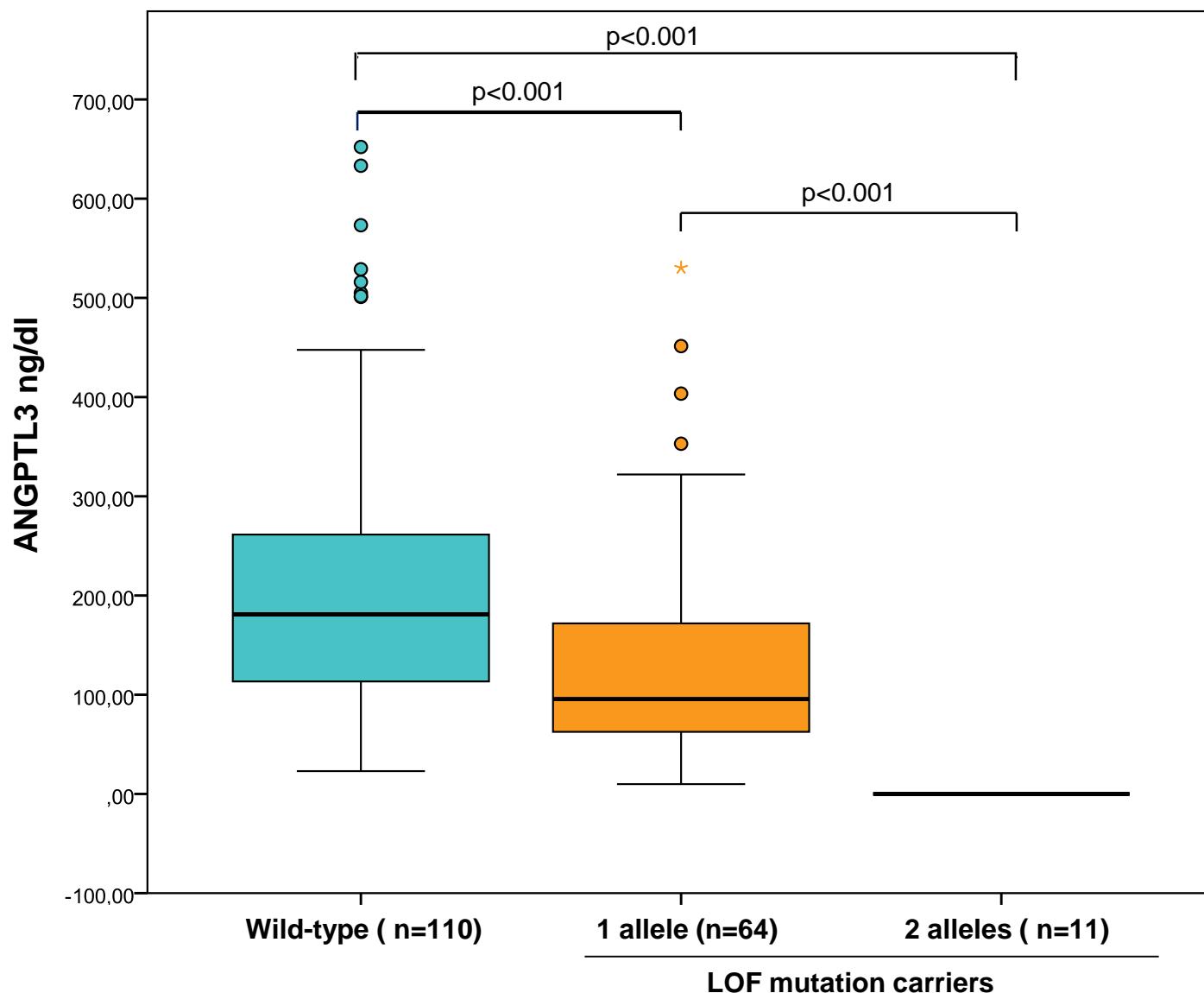
# p<0.05 ##p≤0.01### p<0.001 for comparison between homozygotes vs heterozygotes carriers.

# FHBL2 cohort enrolled in the pooled analysis

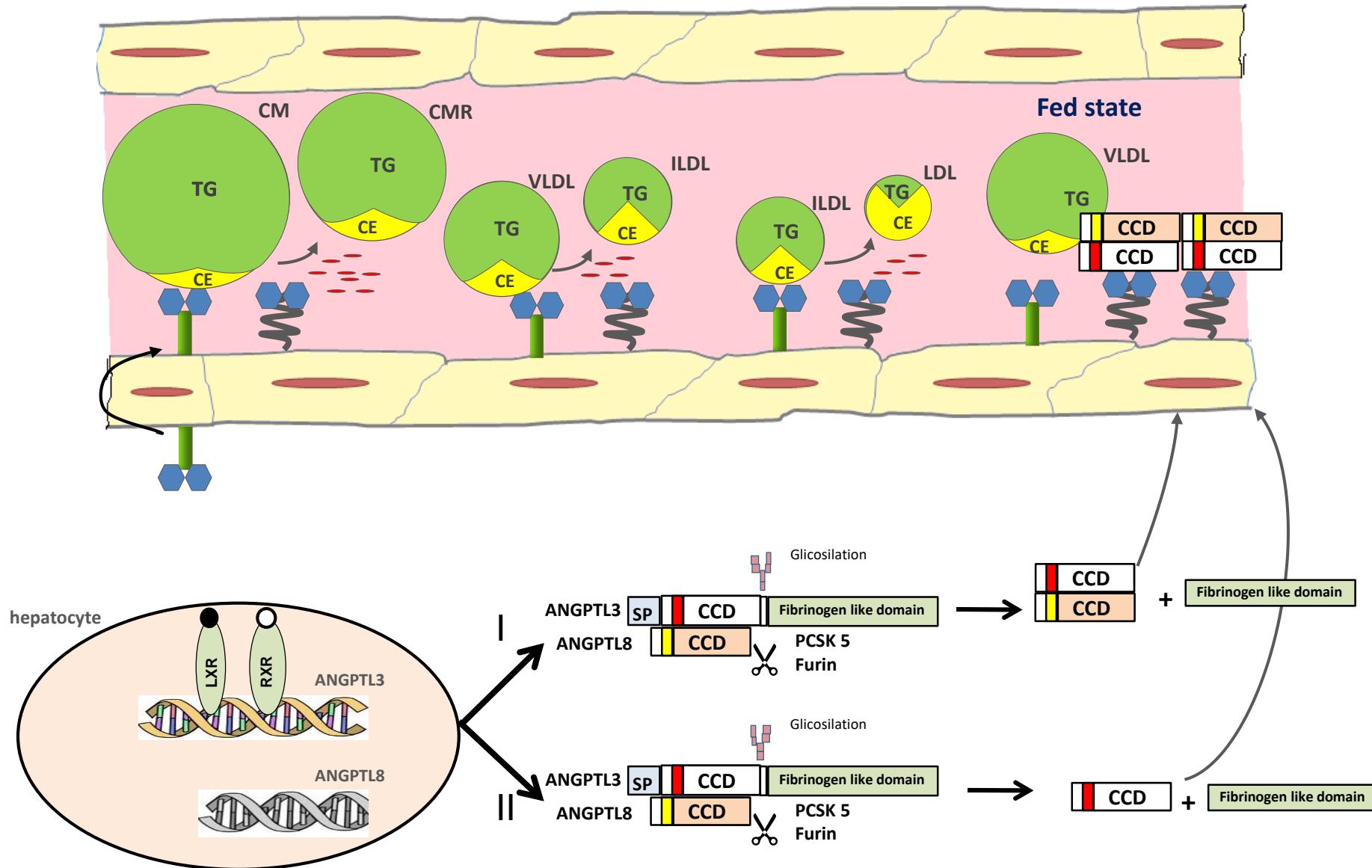
- ❖ 517 subjects (14 homozygous, 8 compound heterozygous, 93 heterozygous) carriers of mutations in the *ANGPTL3* gene and 402 non-carriers controls
- ❖ 31 nuclear families comprising 149 relatives (87 first-degree, 47 second-degree and 15 third-degree relatives) and 45 spouses
- ❖ 14 different LOF mutations in the *ANGPTL3* gene



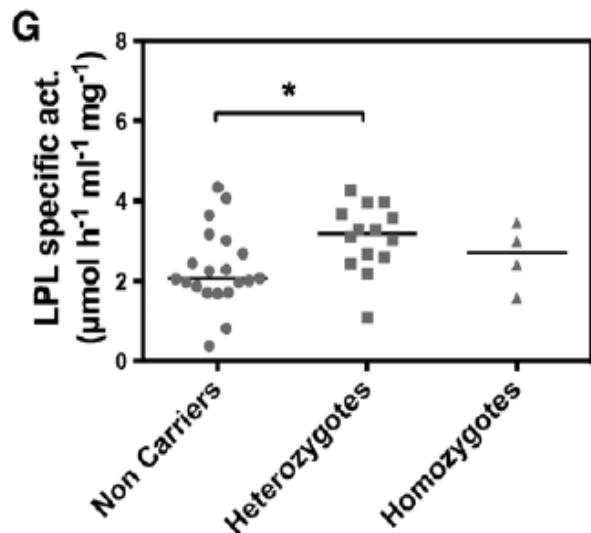
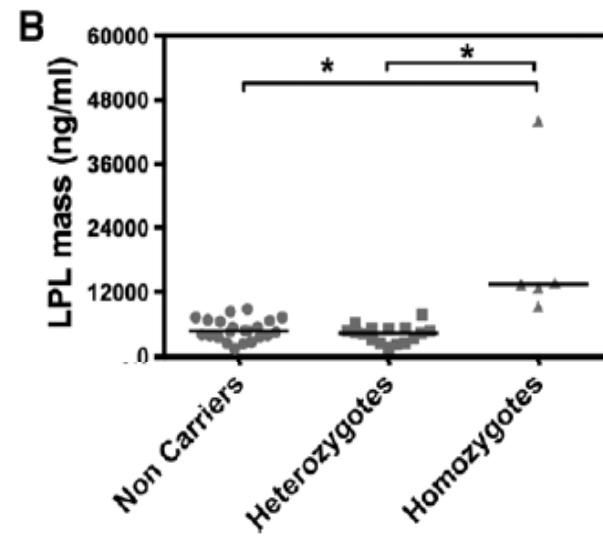
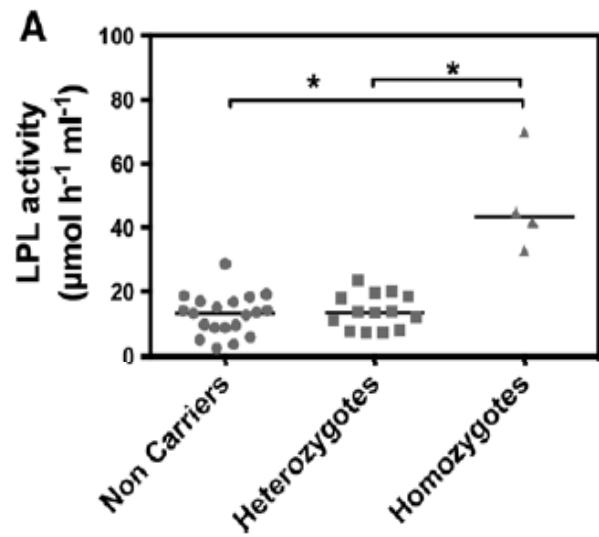
# Plasma levels of ANGPTL3 in carriers of LOF mutations in the *ANGPTL3* gene: pooled analysis



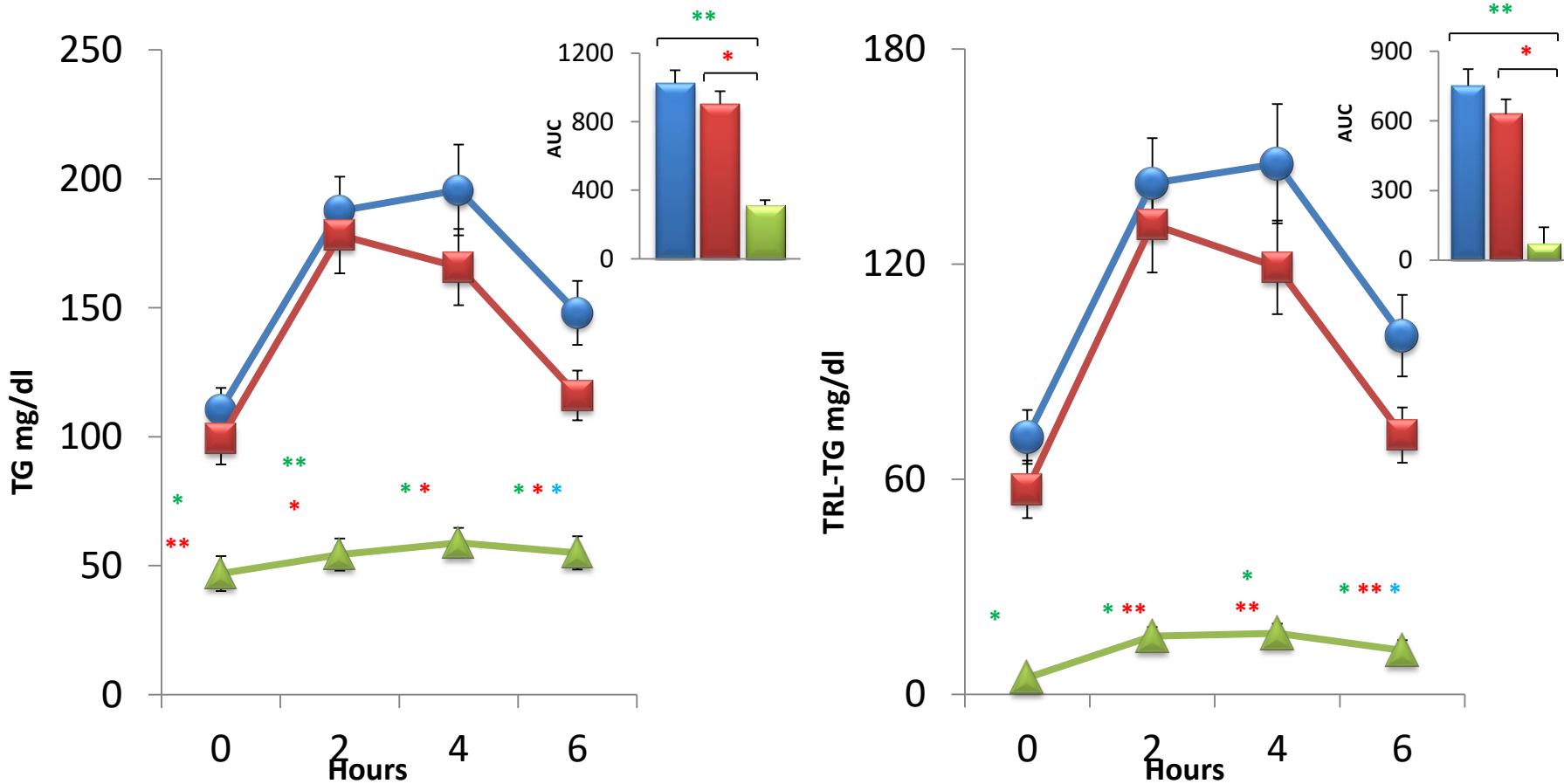
# ANGPTL3/ANGPTL8: proposed mechanism of action on lipoproteins



# Post-heparin lipoprotein lipase mass and activity according to ANGPTL3 p.S17X mutation status



# Postprandial TG change in plasma and in TG-rich lipoproteins



Homozygous (—▲—) and heterozygous (—■—) FHL2 subjects and in controls (—●—).

Bars represent the total areas under the curves (AUC) expressed in mg/dL/h<sup>-1</sup> for each subgroup.

TRL indicated lipoprotein in the d<1.019 g/dL fraction (Chylo, VLDL, IDL)

\*\*P<0.001 and \*P<0.01 homozygotes vs. controls; \*\*P<0.05 and \*P<0.01 homozygotes vs. heterozygotes;

\*P<0.05 heterozygotes vs. controls.

# In vivo metabolism of ApoB, and VLDL Triglycerides in member of the original family with FHL2

**Supplementary Appendix Table 5.** Lipoprotein metabolic studies in selected individuals.

Individual	S17X†	E129X†	VLDL apoB PS, mg/kg	VLDL apoB FCR, pools/h	VLDL apoB PR, $\text{mg} \times \text{kg}^{-1} \times \text{d}^{-1}$	IDL apoB FCR, pools/h	LDL apoB PS, mg/kg	LDL apoB FCR, pools/h	LDL apoB PR, $\text{mg} \times \text{kg}^{-1} \times \text{d}^{-1}$	VLDL TG PS, $\mu\text{mol}/\text{kg}$	VLDL TG FCR, pools/h	VLDL TG PR, $\mu\text{mol} \times \text{kg}^{-1} \times \text{h}^{-1}$
II-4	1	1	0.70	0.51	8.6	1.36	8.0	0.043	8.2	4.1	2.14	8.8
II-6	1	1	0.28	1.26	8.5	2.75	5.5	0.061	8.1	1.5	3.41	5.1
II-10	0	1	0.13	3.5	10.9	4.33	6.5	0.055	9.1	3.1	4.68	14.4
II-15	1	0	1.76	0.48	20.5	0.40	19.3	0.039	17.9	18.8	1.72	32.3
III-1	1	0	0.91	0.81	17.7	0.37	5.5	0.041	6.0	9.1	0.51	4.6
II-12	0	0	0.54	2.33	30.2	0.41	16.9	0.028	11.4	17.8	1.70	30.3
III-11	0	0	1.27	0.69	21.0	0.44	15.3	0.024	9.0	14.7	0.90	13.2
N1*	0	0	1.67	0.64	25.6	0.39	25.2	0.025	15.1	15.3	0.69	10.6
N2*	0	0	0.50	2.57	30.8	0.54	13.2	0.032	10.3	10.6	1.08	11.4
Mean $\pm$ SD	2 mutations		$0.5 \pm 0.3$	$0.9 \pm 0.5$	$8.6 \pm 0.1$	$2.1 \pm 1.0$	$6.8 \pm 1.8$	$0.052 \pm 0.013$	$8.2 \pm 0.1$	$2.8 \pm 1.8$	$2.8 \pm 0.9$	$7.0 \pm 2.6$
	1 mutation		$0.9 \pm 0.8$	$1.6 \pm 1.7$	$16.4 \pm 4.9$	$1.7 \pm 2.3$	$10.4 \pm 7.7$	$0.045 \pm 0.009$	$11.0 \pm 6.2$	$10.3 \pm 7.9$	$2.3 \pm 2.1$	$17.1 \pm 14.0$
	0 mutations		$1.0 \pm 0.6$	$1.6 \pm 1.0$	$26.9 \pm 4.6$	$0.5 \pm 0.07$	$17.7 \pm 5.3$	$0.027 \pm 0.004$	$11.5 \pm 2.6$	$14.6 \pm 3.0$	$1.1 \pm 0.4$	$16.4 \pm 9.3$
<i>P</i> -value, additive model of genetic dosage		0.39	0.57	0.001		0.162	0.05	0.005	0.38	0.03	0.14	0.38

PS indicates pool size; PR, production rate; FCR, fractional catabolic rate.

\* N1 was the spouse of II-6 and was not included in the pedigree; N2 was a son of II-12 and was not included in the pedigree.

† 0 indicates no mutation was present; 1 indicates mutation was present.

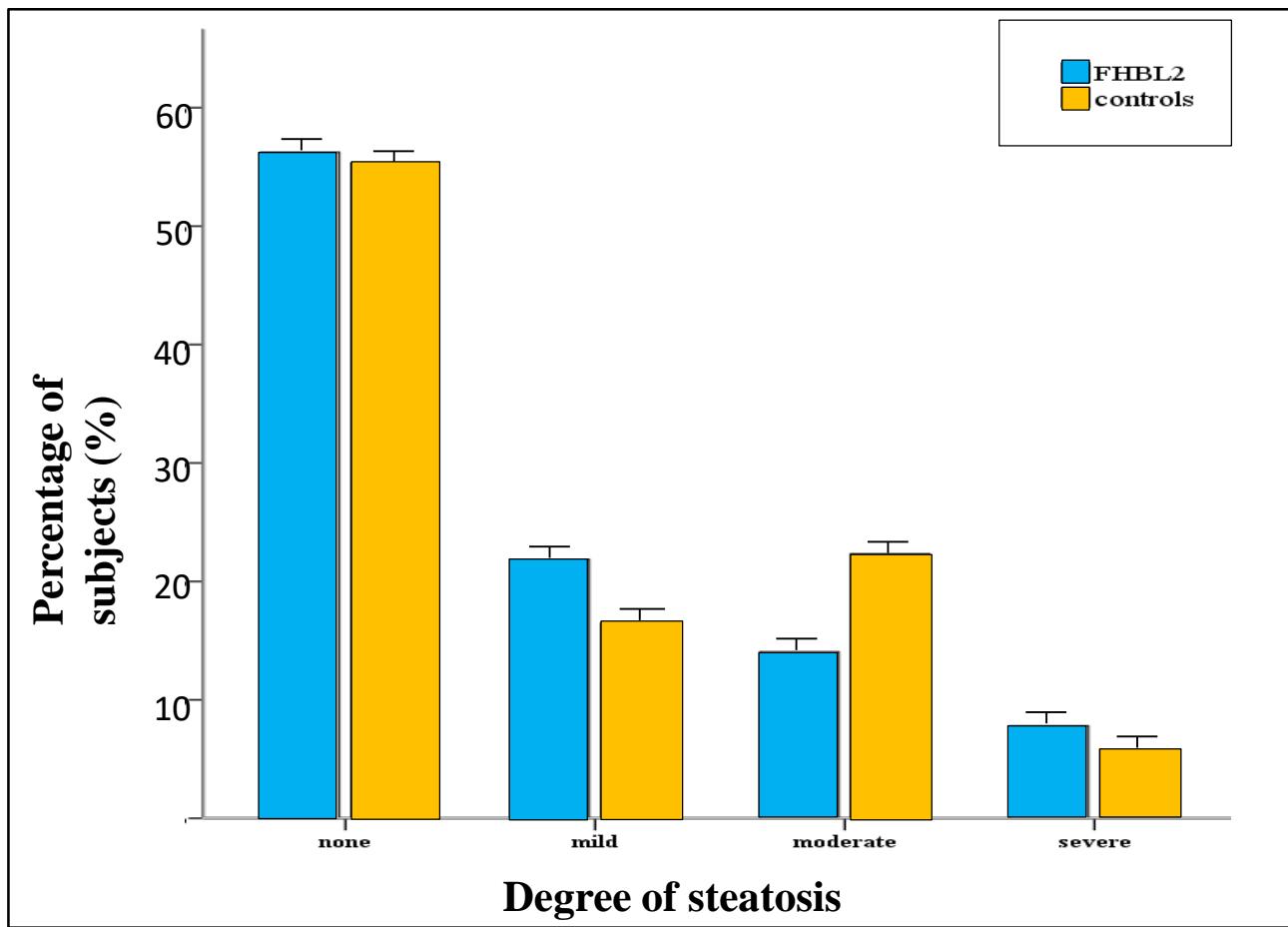
# Demographic and clinical characteristic of FHL2 carriers and non carriers controls.

Variables	FHL2 (n=115)		Non-carriers (n=402)
	Homozygotes / Compound Heterozygotes (n=22)	Heterozygotes (n=93)	
<b>Demographic characteristics</b>			
Age, yrs (ranges)	51.7 ± 20.6 (12 – 88)	46.1 ± 20.9 (10 – 89)	50.4 ± 19.9 (9 – 96)
Sex, n (M/F)	9/13	46/47	187/215
Menopause, n (%)	5 (22.7)	16 (17.2)	108 (26.7)
BMI, (Kg/m <sup>2</sup> )	27.3 ± 5.1 n= 18	27.1 ± 5.0 n=88	27.1 ± 4.8 n= 382
Family history of CVD, n (%)	3 (13.6)	24 (25.0)	104 (25.7)
Family history of Diabetes, n (%)	4 (18.1)	27 (29.0)	127 (31.4)
Smokers, n (%)	5 (22.7)	20 (21.5)	81 (20.0)
Systolic Blood Pressure (mmHg)	131.2 ± 24.2	128.56 ± 20.8	129.0 ± 19.35
Diastolic Blood Pressure (mmHg)	79.7 ± 7.6	79.9 ± 10.2	80.6 ± 10.1
Alcohol consumption, n (%)			
Moderate drinkers	6 (27.3)	43 (46.2)	229 (56.5)
Heavy drinkers	0	3 (3.2)	6 (1.5)
Disease Status, n (%)			
Hypertension	3 (13.6)	20 (21.5)	85 (21.1)
Diabetes mellitus	0	5 (5.3)	36 (9.0)
CVD	0	5 (5.4)	15 (3.7)
Cholelithiasis	0	1 (1.0)	17 (4.2)
Chronic hepatitis	0	1 (1.0)	4 (1.0)
Liver cirrhosis	0	1 (1.0)	0
Hepatic steatosis (FLI)	2 (9)	19 (20.4)	65 (16.2)
Pancreatitis	0	1 (1.0)	0
Current medication, n (%)			
Statins	0	3 (3.2)	40 (9.9)
Aspirin	1 (4.5)	5 (5.4)	31 (7.7)
Antihypertensive	5 (22.7)	16 (17.2)	86 (21.2)
<b>Laboratory measurements</b>			
FBG (mmol/L)	4.9 ± 0.7 n= 16	5.4 ± 1.5 n= 83	5.4 ± 1.3 n= 383
Creatinine (μmol/L)	79.6 ± 18.6*# n= 12	96.4 ± 16.8 n=59	93.7 ± 17.7 n=320
eGFR	74.6 (61.7 – 148.1) n=10	77.9 (62.6 – 86.9) n=58	73.5 (53.4 – 94.9) n=303
ALT (U/L)	26.7 ± 6.8 n=12	27.8 ± 6.9 n=71	29.2 ± 10.0 n=377
AST (U/L)	29.6 ± 10.8 n=12	28.6 ± 15.7 n=71	28.6 ± 13.8 n=71
γGT (U/L)	35.0 ± 13.8 n=6	30.5 ± 24.3 n=65	33.5 ± 27.2 n=201

\*p<0.05 for comparison between non-carriers vs homozygotes carriers.

#p<0.01 for comparison between homozygotes vs heterozygotes carriers

# Prevalence and grade of hepatic stetatosis in 64 ANGPTL3 p.S17X carriers and 107 non-carriers evaluated by echography



44.7% overall prevalence of hepatic stetaosis (any grade)  
in FHBL2 43.7% vs. 44.7% in controls ( $p=0.70$ )

Gravità dei sintomi

- Acantocitosi
- Malassorbimento di lipidi
- Steatorrea
- Deficit di Vit E
- Ritardo di crescita

Ipobetalipoproteinemia  
Familiare (FHBL)  
Ridotta ApoB

**CHYLOMICRON RETENTION  
DISEASE (CRD)**  
*Assenza di ApoB48*

**ABETALIPOPROTEINEMIA (ABL)**  
*Assenza di ApoB*

- Steatosi epatica
- Steatorrea moderata
- Intolleranza ai grassi

- Acantocitosi
- Malassorbimento di lipidi
- Deficit di Vit E
- Retinite pigmentosa
- Neuropatia
- Ritardo di crescita

# LONG-TERM MONITORING OF FHBL SUBJECTS

- ❖ Natural history of FHBL
- ❖ Evolution of fatty liver to more severe liver diseases.
- ❖ Possible relationship with liver cancer
- ❖ Predisposition to gallstones
- ❖ Protection against atherosclerosis