Rare dyslipidaemias, from phenotype to genotype to management

A European Atherosclerosis Society Task Force
Consensus Statement

Robert A. Hegele, Jan Borén, Henry N. Ginsberg, Marcello Arca, Maurizio Averna, Christoph J. Binder, Laura Calabresi, M. John Chapman, Marina Cuchel, Arnold von Eckardstein, Ruth Frikke-Schmidt, Daniel Gaudet, G. Kees Hovingh, Florian Kronenberg, Dieter Lütjohann, Klaus G. Parhofer, Frederick J. Raal, Kausik K. Ray, Alan T. Remaley, Jane K. Stock, Erik S. Stroes, Lale Tokgözoglu, Alberico L. Catapano

Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67

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Review

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

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Lancet Diabetes Endocrinol 2019

Published Online
September 30, 2019
https://doi.org/10.1016/
S2213-8587(19)30264-5

Background to rare diseases

- Global prevalence threshold is ~40 to 50 cases/100,000 people
- Pose a substantial health burden: In Europe, affect up to one in 12, or about 36 million people
- A genetic aetiology is identified in >80% of rare diseases

Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67

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Overview of rare lipoprotein disorders

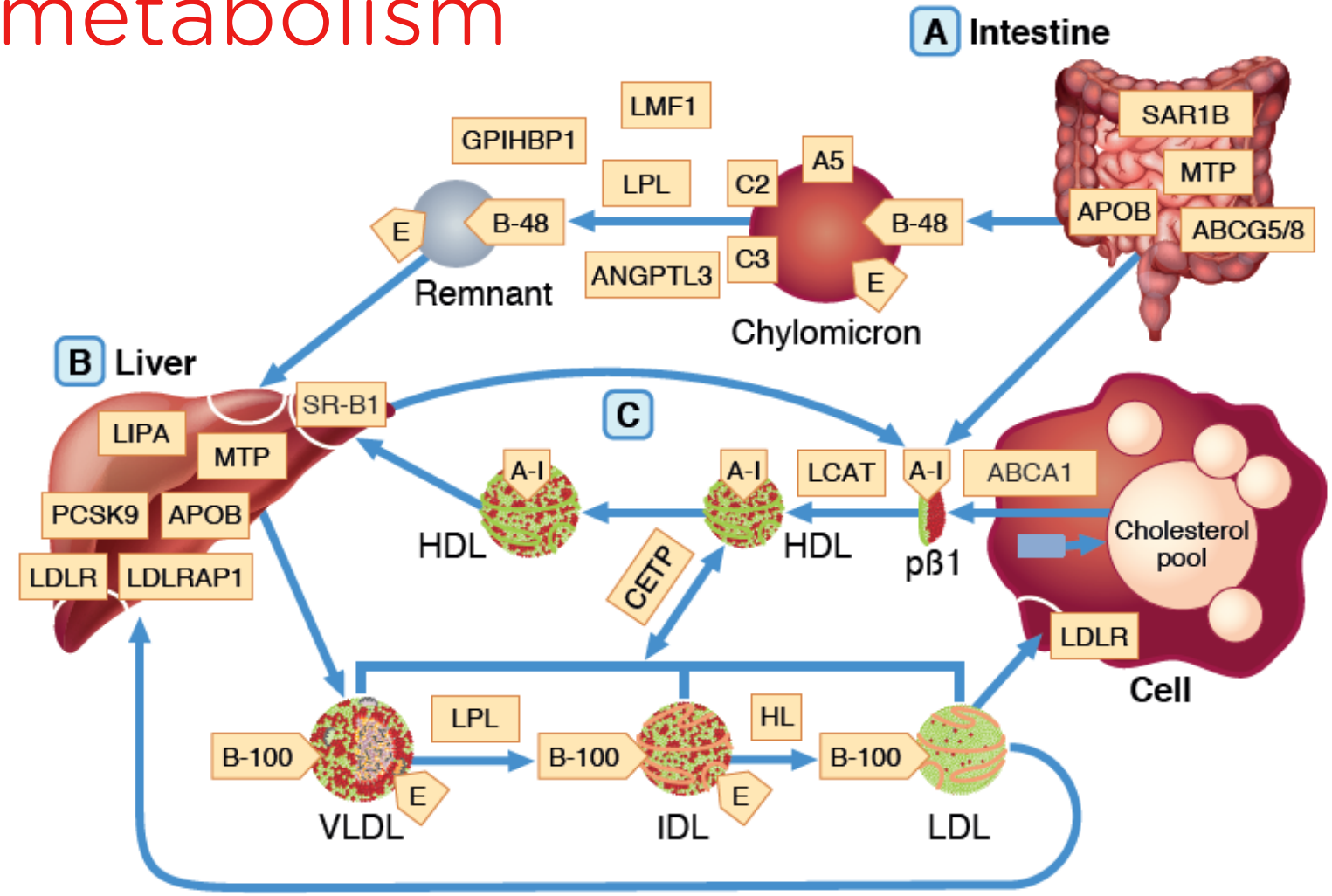
Predominantly monogenic dyslipidaemias:

- ≥25 dyslipidaemias involving 23 genes, with either autosomal dominant, co-dominant, or recessive inheritance
- defined by extreme biochemical deviations with or without physical features

A minority (e.g. polygenic or multifactorial chylomicronaemia) involve an accumulation of common variants with small individual effects

Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67

Background to lipoprotein metabolism



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Abbreviations

APOB apolipoprotein B (B-100, B-48)
A5,C2,C3,EB-48 apolipoproteins AV, C-II, C-III, E and B-48
ABCA1 ATP-binding cassette transporter A1
ABCG5/8 ATP-binding cassette protein 5 and 8
CETP cholesteryl ester transfer protein
GPIHBP1 glycosylphosphatidyl-inositol-anchored high density lipoprotein-binding protein 1
HDL high-density lipoprotein
HL hepatic lipase
IDL intermediate-density lipoprotein
LCAT lecithin-cholesterol acyltransferase
LDL low-density lipoprotein
LDLR LDL receptor
LDLRAP1 LDL receptor-associated protein 1
LIPA lysosomal acid lipase
LMF1 lipase maturation factor 1
LPL lipoprotein lipase
MTP microsomal triglyceride-transfer protein
PCSK9 proprotein convertase subtilisin kexin type 9
SR-B1 scavenger receptor B1
SARB1 Sar1 homolog B GTPase
VLDL very low-density lipoprotein

LDL-related disorders

Hyperlipoproteinaemia (very high LDL-C)

Hyperlipoproteinaemia (very high LDL-C): Modes of inheritance:

Disorder	Inheritance	Gene name	Chromosome
Familial hypercholesterolaemia	ACD	LDLR	19p13
Familial defective apo B-100	ACD	APOB	2p24
Autosomal dominant hypercholesterolaemia type 3	ACD	PCSK9	1p32
Autosomal recessive hypercholesterolaemia	AR	LDLRAP1	1p35
Sitosterolemia (phytosterolaemia)	AR	ABCG5	2p21
Sitosterolemia (phytosterolaemia)	AR	ABCG8	2p21
Atypical dominant hypercholesterolaemia	AD	APOE	19q13
Atypical recessive hypercholesterolaemia	AR	LIPA	10q23
ACD: autosomal codominant (i.e. heterozygotes express an abnormal phenotype about half as extreme as homozygotes)			
AD: autosomal dominant; AR autosomal recessive			

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First steps: Exclude secondary causes

Secondary causes of very high LDL-C include:

- Nephrotic syndrome
- Primary biliary cirrhosis
- Untreated hypothyroidism
- Anorexia
- Some medications

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Homozygous familial hypercholesterolaemia (HoFH)

European Heart Journal (2014) **35**, 2146–2157
doi:10.1093/eurheartj/ehu274

REVIEW

Clinical update

Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society

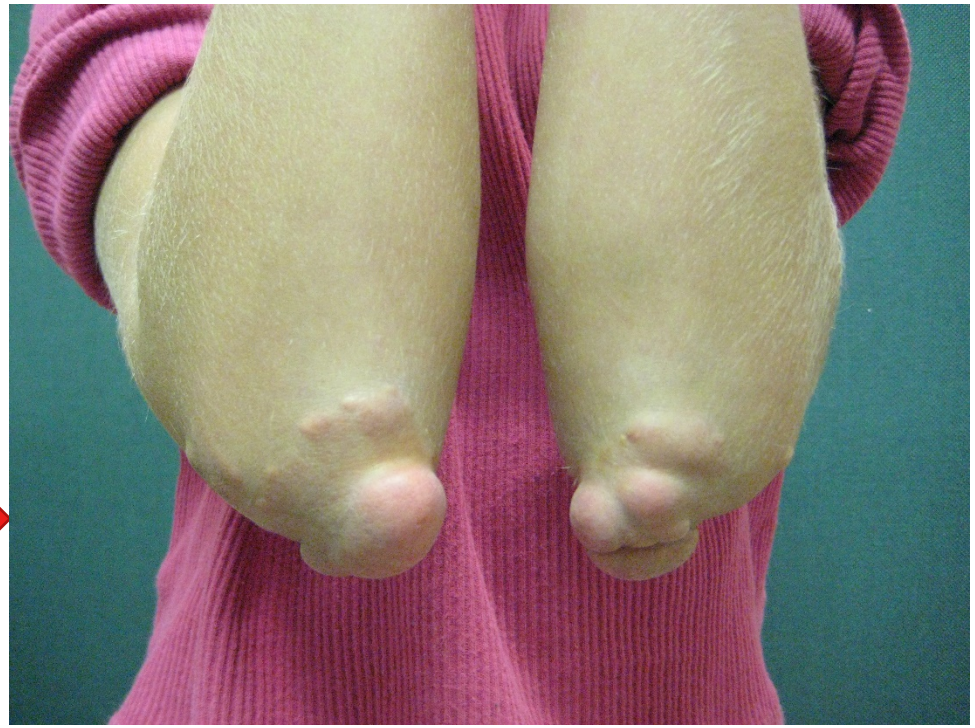
Marina Cuchel*, Eric Bruckert, Henry N. Ginsberg, Frederick J. Raal, Raul D. Santos, Robert A. Hegele, Jan Albert Kuivenhoven, Børge G. Nordestgaard, Olivier S. Descamps, Elisabeth Steinhagen-Thiessen, Anne Tybjærg-Hansen, Gerald F. Watts, Maurizio Averna, Catherine Boileau, Jan Borén, Alberico L. Catapano, Joep C. Defesche, G. Kees Hovingh, Steve E. Humphries, Petri T. Kovanen, Luis Masana, Päivi Pajukanta, Klaus G. Parhofer, Kausik K. Ray, Anton F. H. Stalenhoef, Erik Stroes, Marja-Riitta Taskinen, Albert Wiegman, Olov Wiklund, and M. John Chapman, for the European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolaemia†

Cuchel M et al, Eur Heart J 2014; 35:2146-2157

HoFH

Historical definition:

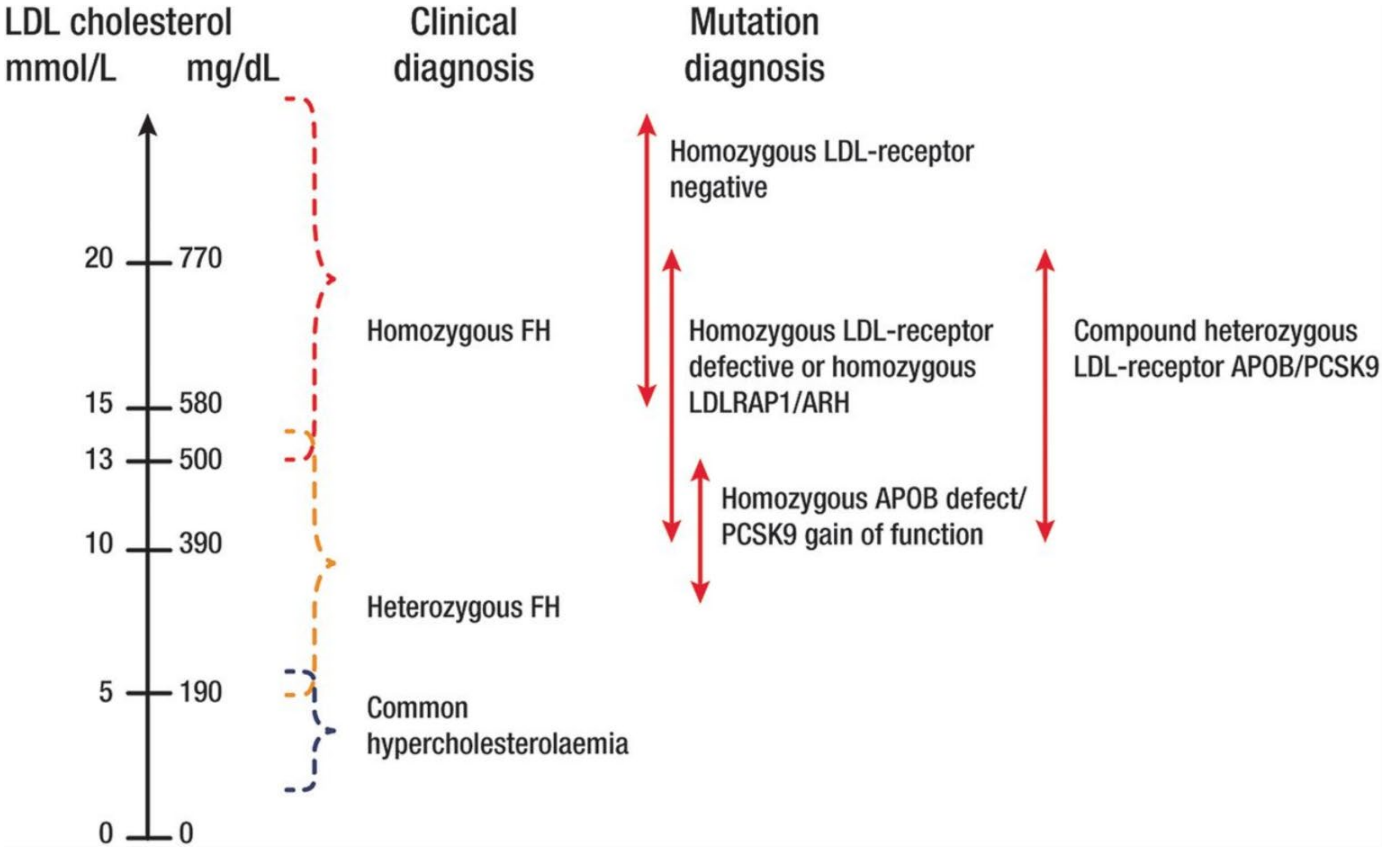
- Treated LDL-C >8 mmol/L (>300 mg/dL) OR
- Untreated LDL-C >10 mmol/L (>400 mg/dL) WITH
- Cutaneous or tendon xanthomas before age of 10 years



Prevalence: 1:160,000 - 300,000 people

Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67. Photo courtesy Prof. Derick Raal.

Genetic variability confers phenotypic variability in HoFH

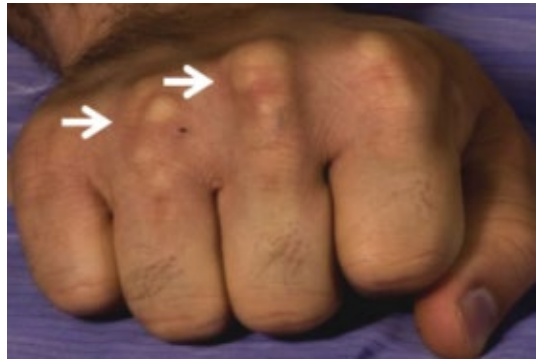


Nordestgaard BG et al. Eur Heart J 2013;34:3478-90a.

Diagnosis of HoFH

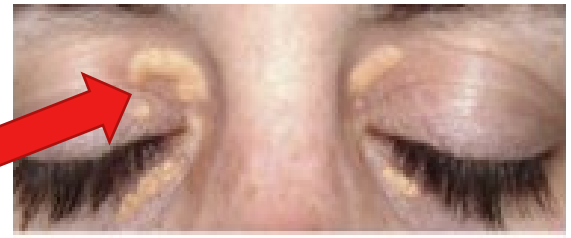
- **Mainly depends on clinical assessment**: Scoring systems (e.g. Dutch Lipid Clinic Network score) can be helpful

Clinical presentations of HoFH

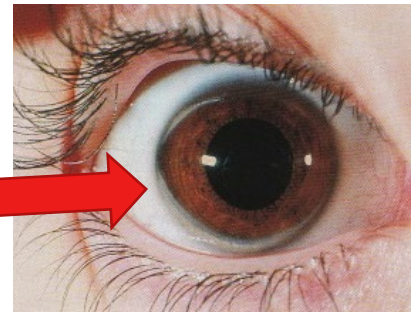


Extensor tendon xanthomas

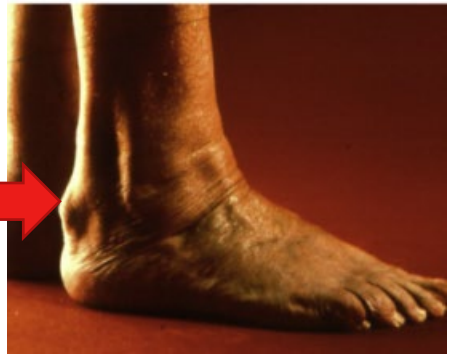
Xanthelasmas



Corneal arcus



Achilles tendon xanthomatosis



Davignon J, Dufour R. Primary hyperlipidemias. Oxford: Clinical Publishing, 2007.
Genest J et al. Can J Cardiol 2014; 30: 1471–81.
Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67

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Diagnosis of HoFH: Genotyping

- *LDLR* gene mutations are most prevalent, accounting for >80% of cases: >2,300 unique FH-causing mutations
- *APOB* gene: >50 likely pathogenic mutations
- *PCSK9* gene: >30 gain-of-function mutations

Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67

Management of HoFH

Treatment intensity should be targeted to LDL-C level as this determines risk for atherosclerotic cardiovascular disease.

Current treatment strategies:

- Maximally tolerated statin, ezetimibe, in addition to diet and lifestyle
- Lipoprotein apheresis
- PCSK9 monoclonal antibody therapy: ineffective in individuals with two null *LDLR* mutations
- Lomitapide: adherence to low-fat diet and side effects (hepatic steatosis) are often problematic

Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67:

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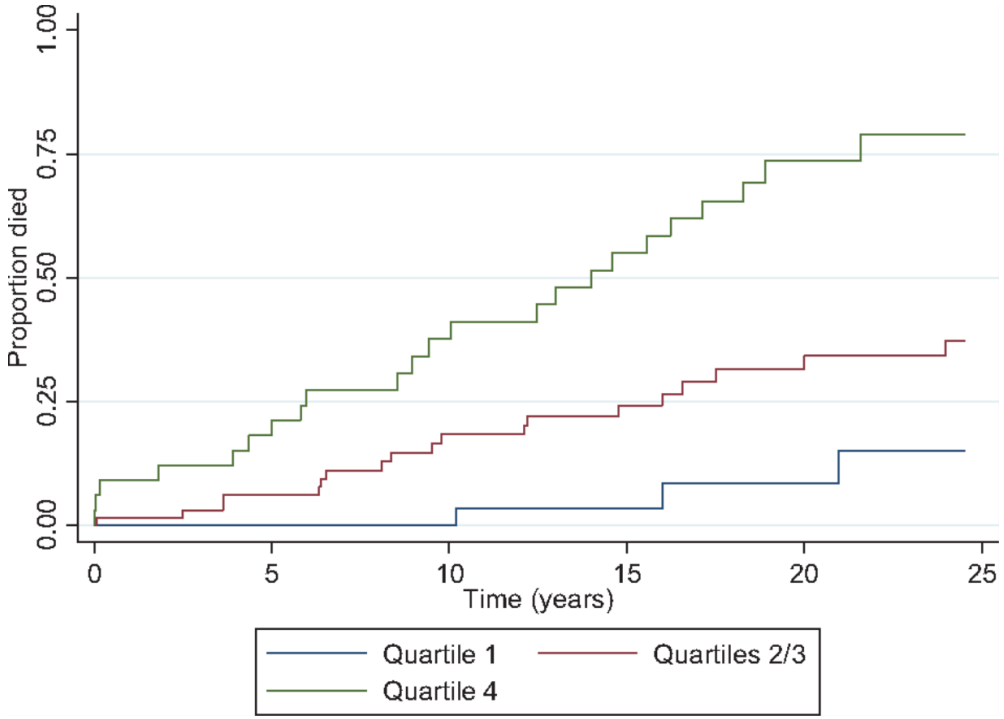
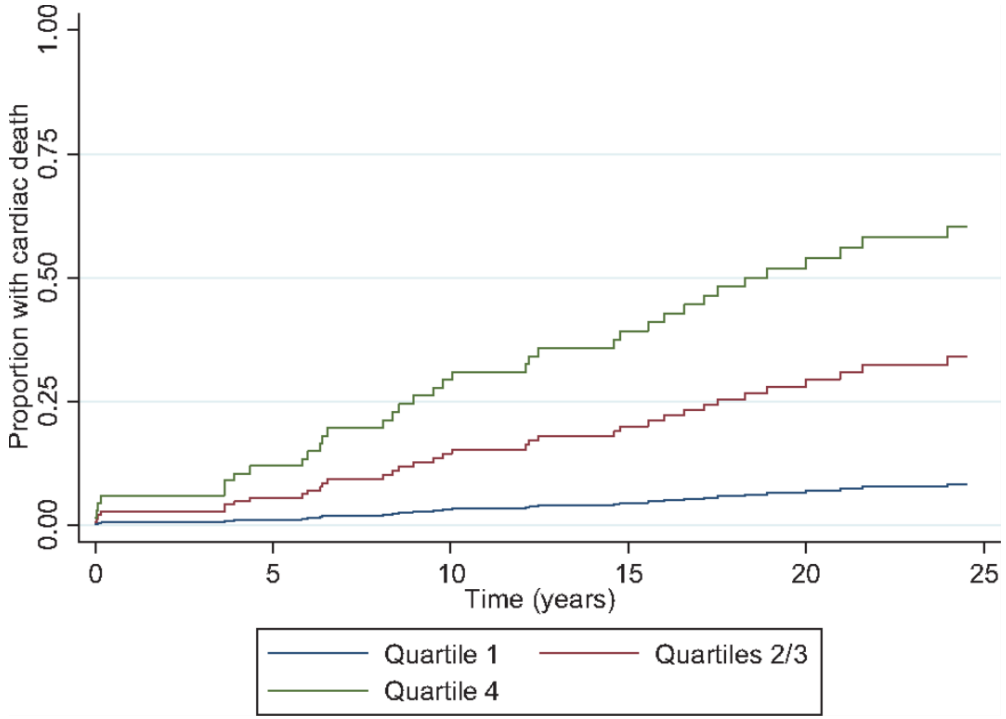
HoFH: Survival depends on on-treatment cholesterol





Thompson et al. Eur Heart J. 2017;39(14):1162-1168.

Other conditions to consider: Beta-sitosterolaemia (phytosterolaemia)

- Atypical xanthomatosis with elevated levels of plant sterols and stanols (phytosterols); LDL-C may be elevated but less than for HoFH
- Variable susceptibility to early atherosclerotic cardiovascular disease
- Treatment: limit intake of plant sterols, with ezetimibe or a bile acid sequestrant

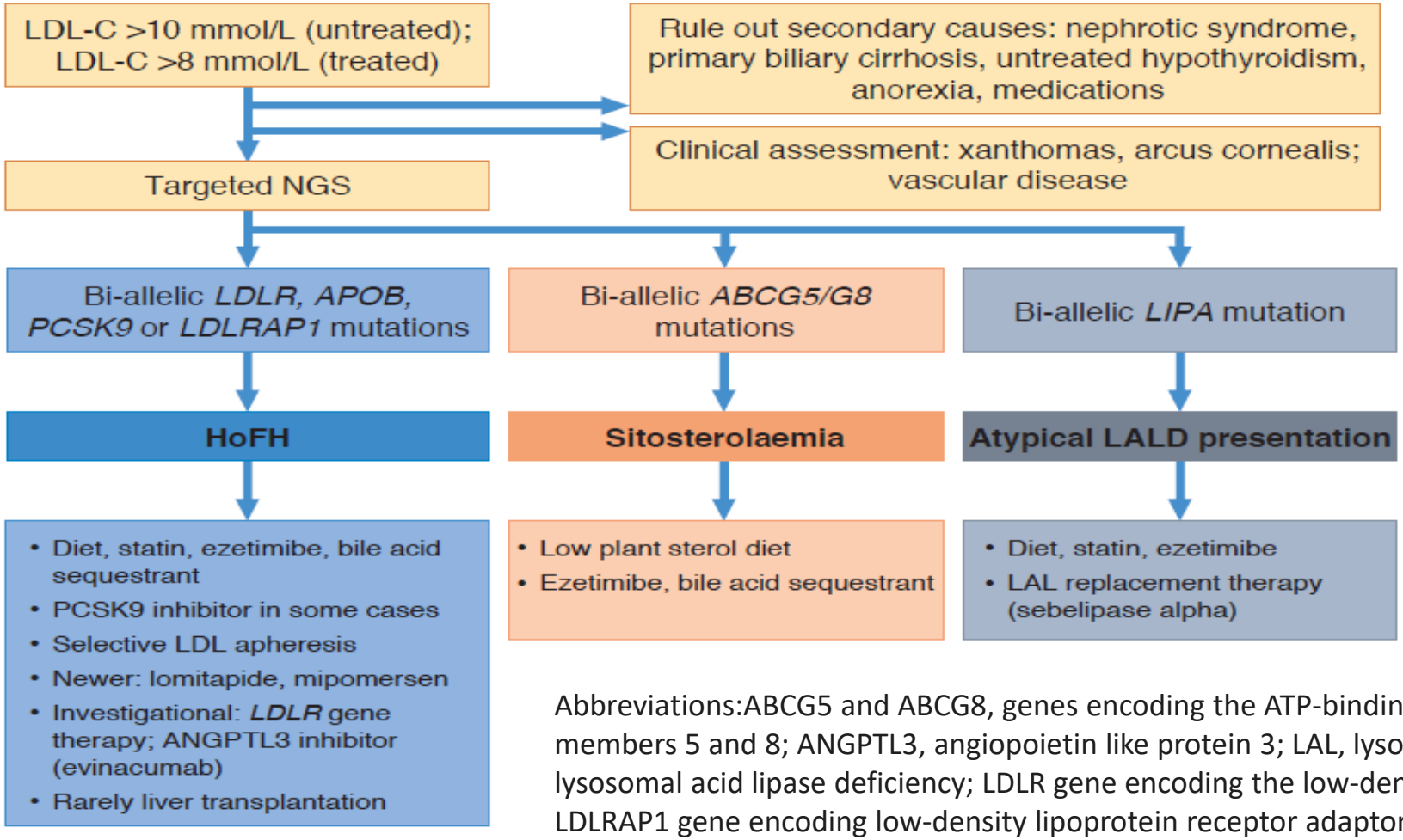
Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67:

Other conditions to consider: Lysosomal acid lipase deficiency (LALD)

- Also referred to as cholesterol ester storage disease or, in children, Wolman disease
- Definitive diagnosis: blood test for LAL activity or DNA sequencing
- Treatment: diet, statin and ezetimibe, with LAL replacement therapy (sebelipase alfa)

Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67

Management of very high LDL-C



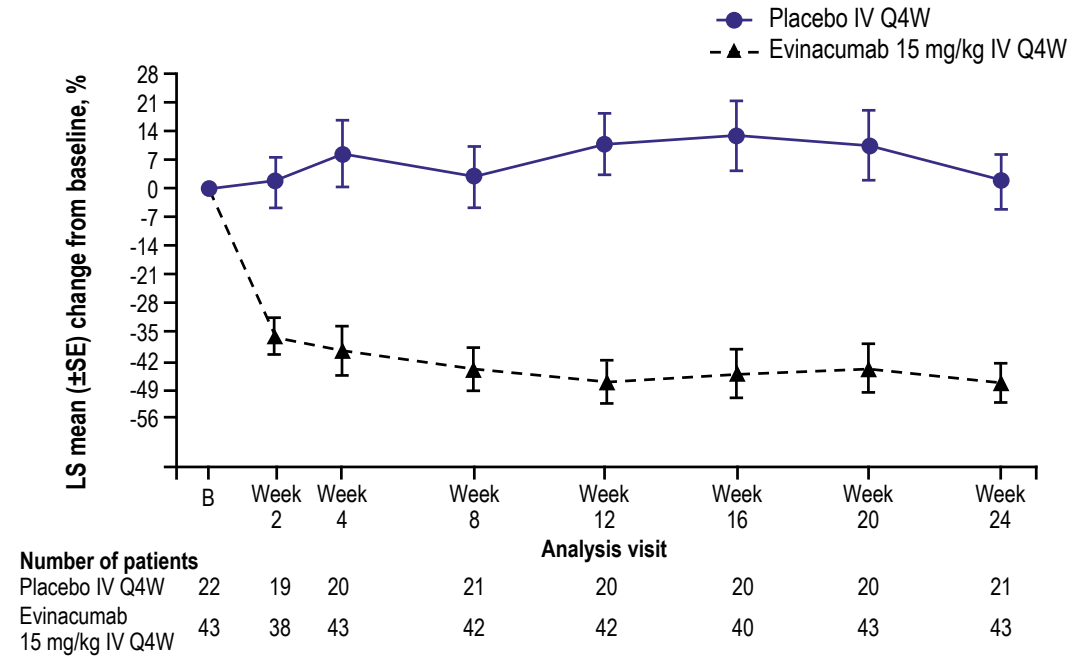
Abbreviations:ABCG5 and ABCG8, genes encoding the ATP-binding cassette sub-family G members 5 and 8; ANGPTL3, angiopoietin like protein 3; LAL, lysosomal acid lipase; LALD, lysosomal acid lipase deficiency; LDLR gene encoding the low-density lipoprotein receptor; LDLRAP1 gene encoding low-density lipoprotein receptor adaptor protein 1; LIPA gene encoding lysosomal acid lipase; NGS, next generation sequencing; PCSK9 gene encoding the enzyme proprotein convertase subtilisin/kexin type 9

Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67:

HoFH: Emerging therapies

- Evinacumab, a monoclonal antibody to ANGPTL3*
- LDLR gene therapy

* Angiopoietin-like 3 protein



Primary endpoint
Percent change in LDL-C at Week 24 (LS mean [SE]):

Evinacumab –47.1% (4.6)
Placebo +1.9% (6.5)
Difference –49.0% (8.0)
P<0.0001

LDL-related disorders

Hypolipoproteinaemia (very low LDL-C)

Hypolipoproteinaemia (LDL-C <1.0 mmol/L): Modes of inheritance

Disorder	Inheritance	Gene name	Chromosome
Abetalipoproteinaemia	AR	MTTP	4q23
Homozygous hypobetalipoproteinaemia	ACD	APOB	2p24
Chylomicron retention disease (Anderson disease)	AR	SAR1B	5q31
Familial combined hypolipidaemia	ACD	ANGPTL3	1p31
Hypobetalipoproteinaemia, PCSK9 deficiency	ACD	PCSK9	1p32
ACD: autosomal codominant (i.e. heterozygotes express an abnormal phenotype about half as extreme as homozygotes)			
AD: autosomal dominant; AR autosomal recessive			

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First steps: Exclude secondary causes

- Chronic liver disease
- Chronic pancreatitis
- Cystic fibrosis
- End-stage renal disease
- Hyperthyroidism
- Cachexia and malabsorption
- Malnutrition
- Vegan diet

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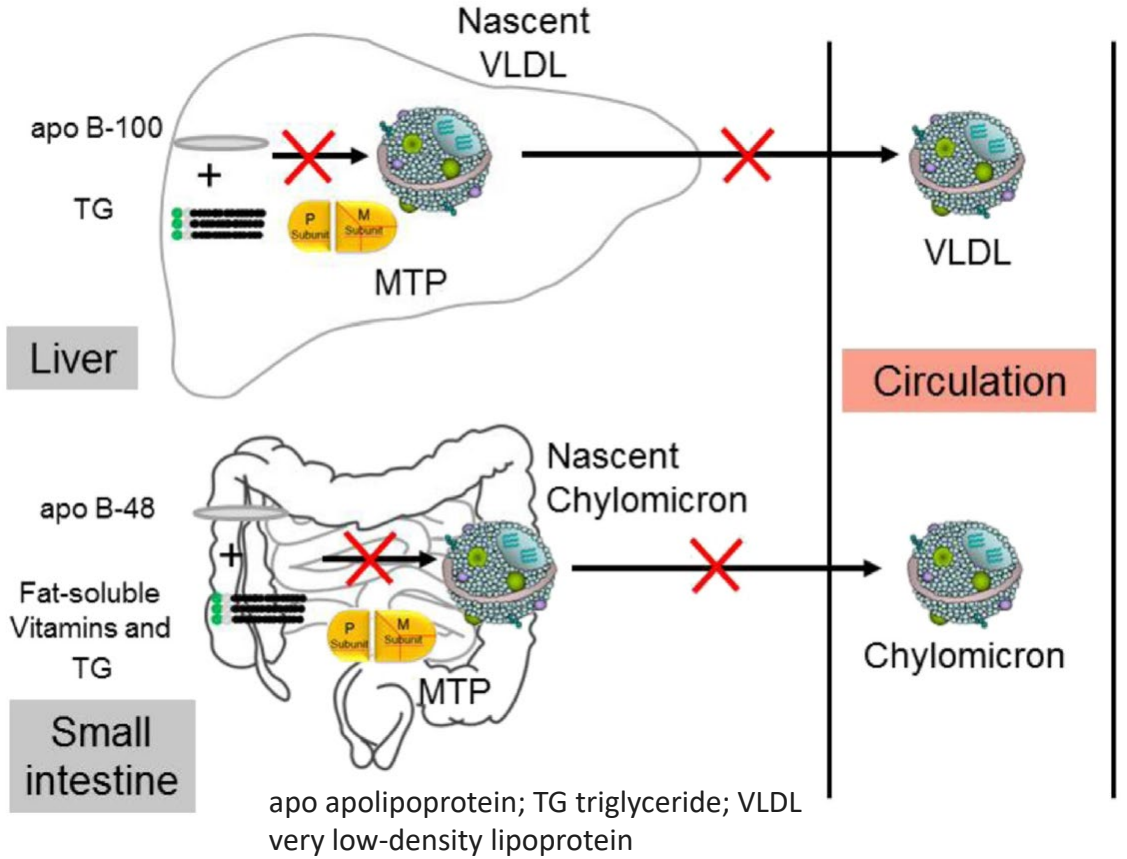
Abetalipoproteinaemia (ABL) (also known as Bassen–Kornzweig syndrome)

- Lack of VLDL and chylomicron production due to loss-of-function mutations in the *MTTP* gene (encoding microsomal triglyceride transfer protein, MTP)
- >30 *MTTP* mutations reported to date
- Undetectable plasma levels of LDL-C and apo B
- TG and total cholesterol are also very low (<0.33 mmol/L or 30 mg/dL)
- Note: Parents of ABL patients have normal lipid profiles

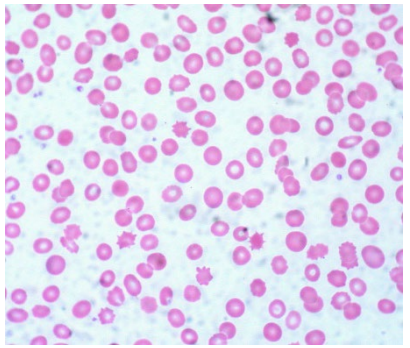


apo apolipoprotein; TG triglyceride; VLDL very low-density lipoprotein

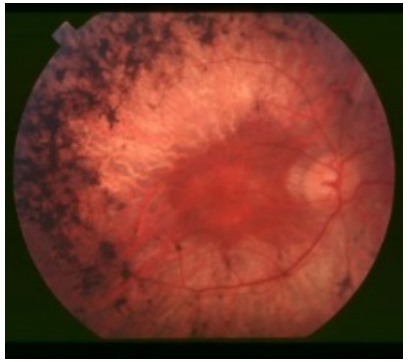
Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67; Figure courtesy of Prof. Jan Boren

Abetalipoproteinaemia (ABL) Clinical presentation

- Variable severity , depending on *MTTP* mutation
- In childhood, may include: **acanthocytosis** mild anaemia from birth, fat malabsorption, and growth failure
- Symptoms of fat soluble vitamin deficiency: night blindness, atypical **retinitis pigmentosa** osteomalacia or rickets, posterior column signs, spinocerebellar ataxia, peripheral neuropathy, and prolonged prothrombin time



Acanthocytes from peripheral blood on light microscopy



Atypical retinitis pigmentosa on fundoscopy

Hamel C Orphanet J Rare Dis 2006; 1: 40;
Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67.
Photos courtesy of Prof. Arnold von Eckardstein

Homozygous familial hypobetalipoproteinaemia (FHBL)

- Mutations in the *APOB* gene either abolish or interfere with the translation of full-length apolipoprotein B (apoB), resulting in truncated forms with less lipid content. Also decreased secretion of very low-density lipoprotein (VLDL), and increased catabolism of VLDL and LDL.
- >60 pathogenic *APOB* mutations reported to date
- Very low levels of apoB (<5th percentile for age and sex) and LDL-C (usually <1.0 mmol/L or <38.7 mg/dL)
- Clinical features are indistinguishable from ABL
- Note: Heterozygous parents of homozygous FHBL patients have depressed LDL-C levels

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Chylomicron retention disease (CRD) (also known as Anderson disease)

- Intestinal defect in lipid transport due to a failure of chylomicron formation in enterocytes
- Triglyceride levels are relatively normal, but absence of apoB-48 and chylomicrons after a fat load
- May be considered if there is failure to thrive in infancy, together with severe malabsorption with steatorrhoea, and fat soluble vitamin deficiency
- Less severe eye defects than in ABL
- Note: heterozygous parents of CRD patients have normal lipid profiles

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Management of ABL, FHBL and chylomicron retention disease

Early diagnosis and treatment are essential to prevent long term ophthalmologic and neurologic complications

Three common principles of management

- Low-fat diet to prevent steatorrhoea
- Supplementation with essential fatty acids
- High oral doses of vitamins A, D, E and K

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Other disorders associated with LDL-C levels <1.0 mmol/L

Familial combined hypolipidaemia (FCH): loss-of-function mutations in *ANGPTL3*

- Reduced levels of all plasma lipoproteins

PCSK9 deficiency: loss-of-function mutations in *PCSK9* (>30 reported to date)

- Heterozygotes show ~40% lower LDL-C levels compared with normal
- Homozygotes show very low LDL-C levels

No clinical phenotype or specific treatment for either condition

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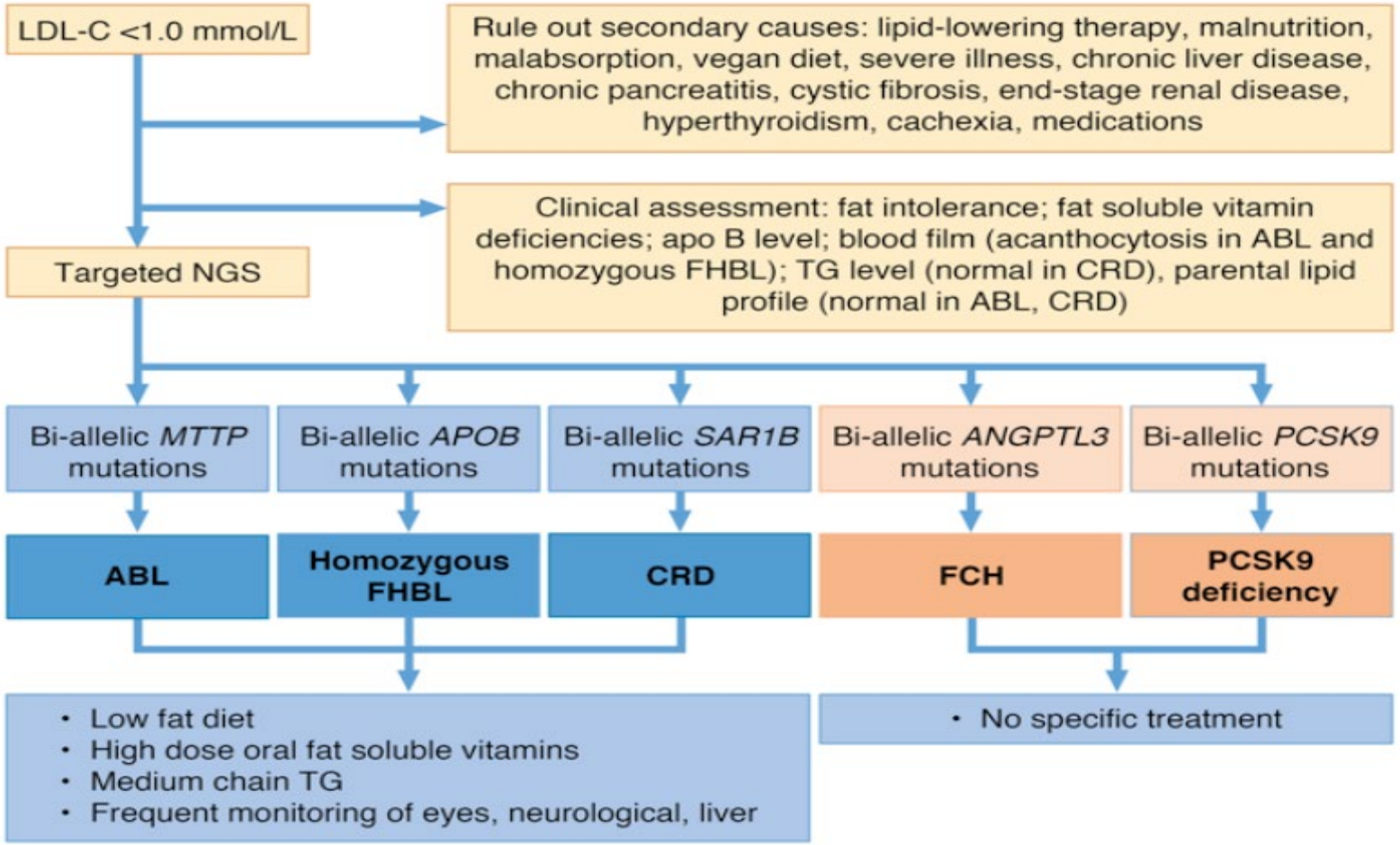
Management of very low LDL-C



Abbreviations:ABL, abetalipoproteinaemia; ANGPTL3 gene encoding angiopoietin-like 3; APOB gene encoding apolipoprotein B; CRD, chylomicron retention disease; FCH, familial combined hypolipidaemia; FHBL, familial hypobetalipoproteinaemia; LDL-C low-density lipoprotein cholesterol; MTTP gene encoding microsomal triglyceride transfer protein; NGS, next generation sequencing; PCSK9 gene encoding the enzyme proprotein convertase subtilisin/kexin type 9; SAR1B gene encoding GTP-binding protein SAR1b; TG triglycerides

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TG-related disorders

Severe hypertriglyceridaemia

Definition

- Triglycerides (TG) >10 mmol/L (>885 mg/dL)
- May be polygenic (multifactorial) or monogenic.
- Most people with severe hypertriglyceridaemia have an accumulation of TG-raising polymorphisms, which cumulatively increase susceptibility to this disorder. Secondary non-genetic factors exacerbate presentation.

About 1–2% of adults with severe hypertriglyceridaemia have a monogenic cause

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Disorders characterised by very high TG levels: Modes of inheritance

Disorder	Inheritance	Gene name	Chromosome
Monogenic chylomicronemia			
- LPL deficiency	AR	LPL	8p22
- Apo C-II deficiency	AR	APOC2	19q13
- Apo A-V deficiency	AR	APOA5	11q23
- Lipase maturation factor 1 deficiency	AR	LMF1	16p13
- GPIHBP1 deficiency	AR	GPIHBP1	8q24
Infantile hypertriglyceridaemia, transient	AR	GPD1	12q12
Dysbetalipoproteinaemia	Complex	APOE	19q13
AR autosomal recessive			

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Five key players in triglyceride catabolism

- **Lipoprotein lipase (LPL):** lipolysis of chylomicrons and VLDL
- **Apolipprotein (apo) C-II:** co-activator of LPL
- **Apo A-V:** thought to facilitate the interaction of chylomicrons and VLDL with LPL at the surface of the capillary endothelium
- **Lipase maturation factor 1 (LMF1):** required for proper folding and intracellular trafficking of nascent LPL
- **Glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1):** critical role in the lipolytic processing of chylomicrons

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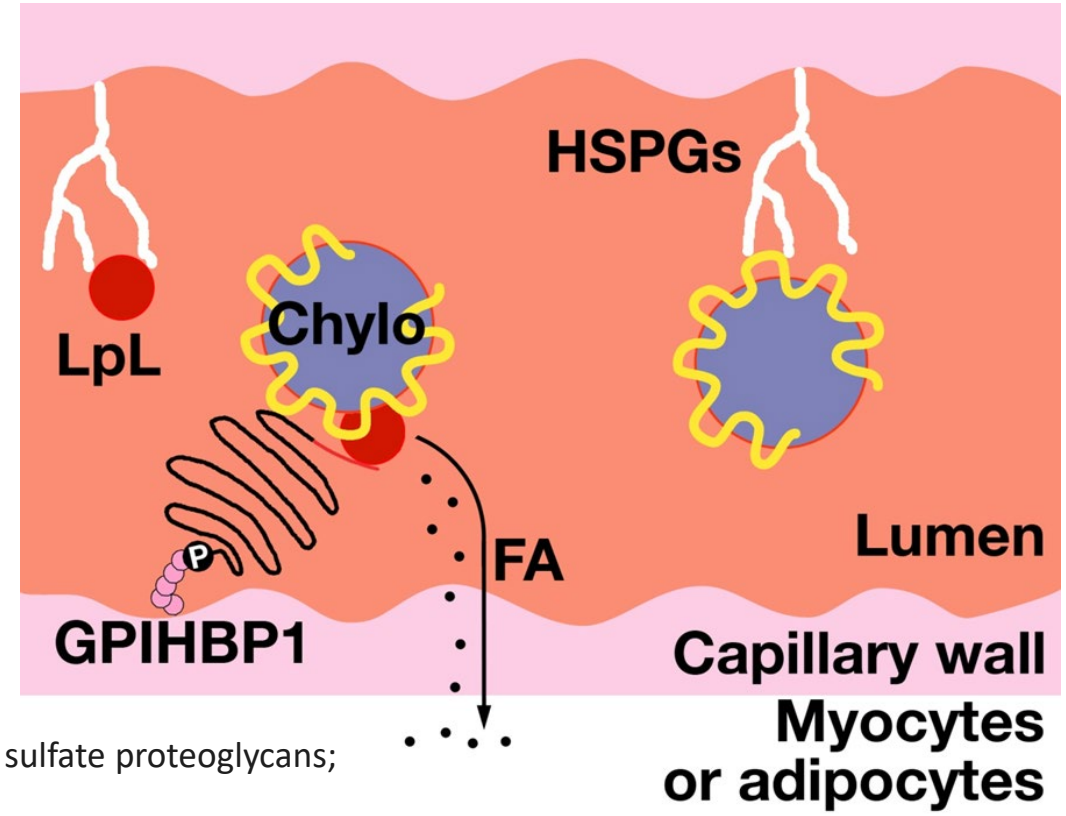
Glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1)

- Required for translocation of newly secreted LPL across the endothelial layer of capillaries and stabilisation of the enzyme on the endothelial luminal surface



Chylo chylomicron; HSPGs heparan sulfate proteoglycans; FA fatty acids; LPL lipoprotein lipase

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Monogenic chylomicronaemia

Mutations in genes encoding these 5 key players in triglyceride catabolism are causal:

- ***LPL* mutations are most common, present in >80% of individuals (>100 mutations)**
- *GPIHBP1* mutations are second most common cause, in 5–10% of cases
- *APOC2* encoding apo C-II
- *APOA5* encoding apo A-V

} causative mutations in 2–5% of cases

- *LMF1* mutations are causative in 1–2% of cases

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Other causes of monogenic chylomicronaemia

- GPD1 (glycerol-3-phosphate dehydrogenase 1): complete loss reported in transient childhood hypertriglyceridaemia
- Other genes implicated include:

  CREBH, encoding transcription factor cyclic AMP-responsive element-binding protein H

  GCKR, encoding glucokinase regulatory protein

  Both also contribute to polygenic chylomicronaemia

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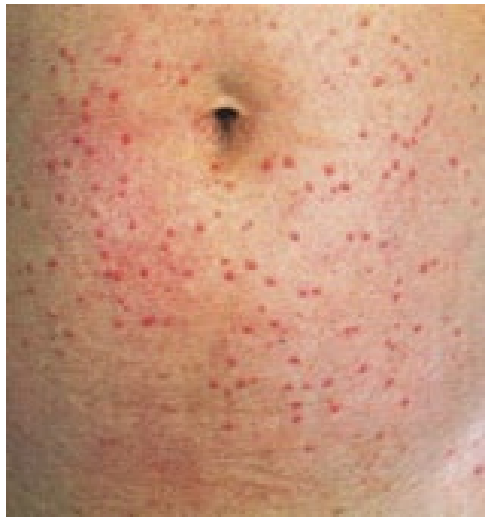
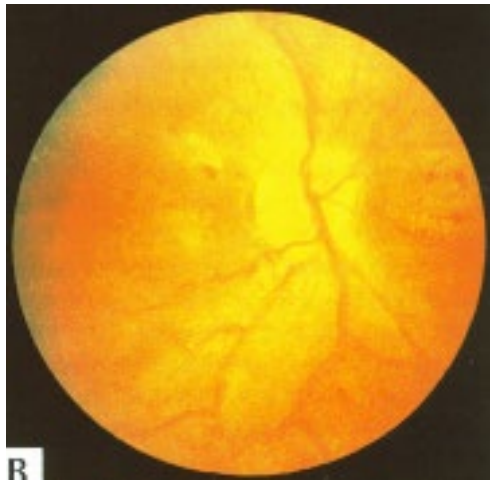
Clinical features of chylomicronaemia syndrome

- Abdominal pain
- Recurrent acute pancreatitis
- Hepatosplenomegaly
- Eruptive xanthomatosis
- Lipaemia retinalis
- Fatigue
- Memory loss
- Depression
- Vomiting and diarrhoea
- Proteinuria
- Anaemia





Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67.
Davignon J, Dufour R. Primary hyperlipidemias. Oxford: Clinical Publishing, 2007.
Photo of lipaemia retinalis courtesy of Prof. Henry Ginsberg

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Diagnosis of monogenic chylomicronaemia

- **Consider if triglycerides >10 mmol/L (>875 mg/dL); low plasma apoB (<0.75 g/L) will differentiate from multifactorial chylomicronaemia**
- Usually presents in childhood (failure to thrive); in older individuals, often diagnosed on routine blood testing
- History of severe hypertriglyceridaemia in a sibling indicates a strong genetic basis
- Genetic testing (LPL, APOC2, APOA5, GPIHBP1, LMF1)
- Polygenic score for hypertriglyceridaemia

Screening of siblings of an affected child is obligatory

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Exacerbating factors

For both monogenic and polygenic chylomicronaemia, the risk of pancreatitis is exacerbated by:

- High-fat foods
- Alcohol
- Oestrogen-containing medications
- Medications increasing VLDL secretion (e.g. steroids)
- Pregnancy
- Obesity and insulin resistance
- Diabetes
- Hypothyroidism

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Long-term management of chylomicronaemia

- Low-fat diet (<10% of calories); supplement with medium chain fatty acids for diet variety
- Avoid alcohol
- Reduce intake of high glycaemic foods
- High dose (4g) omega-3 fatty acids
- Fibrates

} Not effective in monogenic chylomicronaemia

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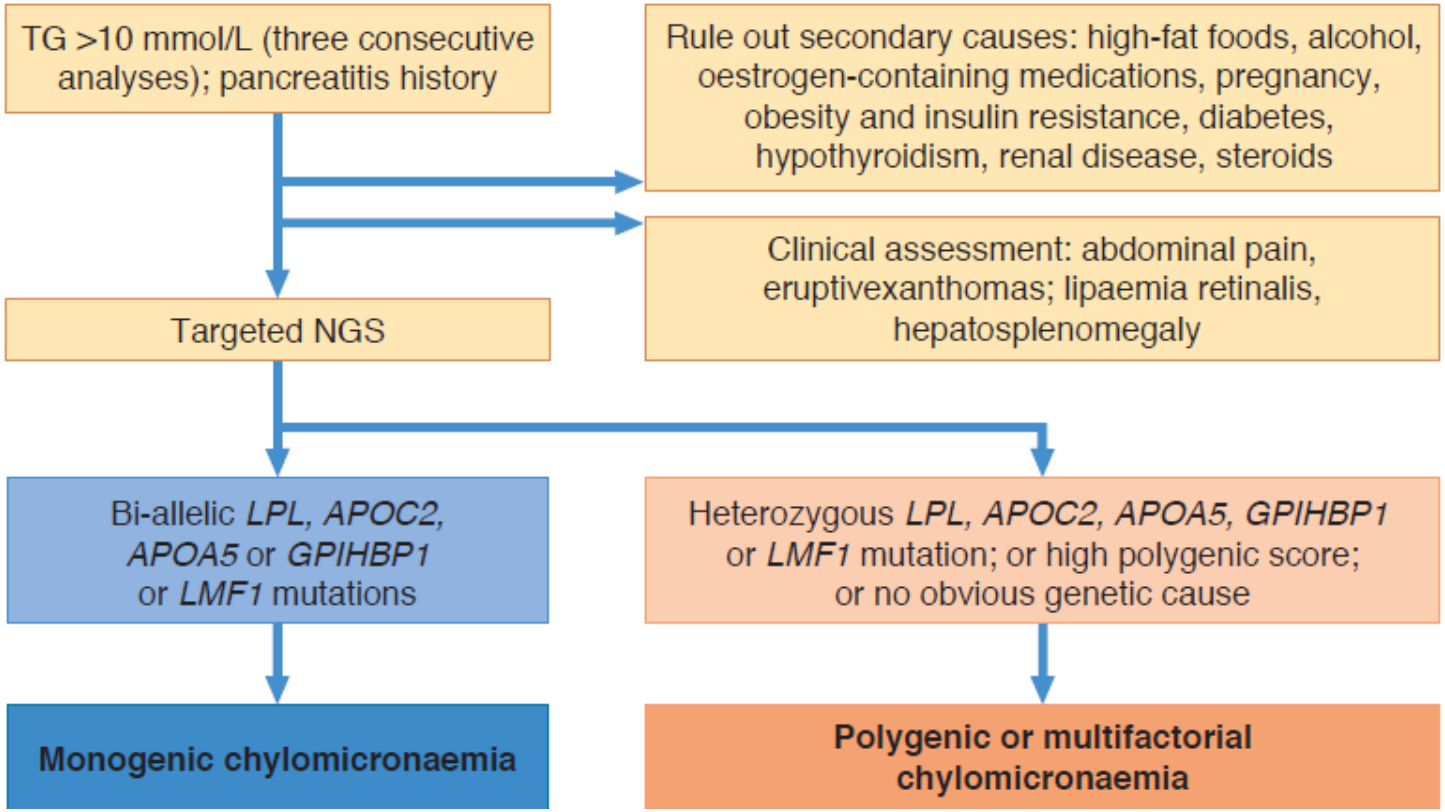
Management of chylomicronaemia



Abbrevations: APOA5, gene encoding apolipoprotein (apo) A-V; APOC2, gene encoding apo C-II; abetalipoproteinaemia; GPIHBP1, gene encoding glycosylphosphatidylinositol-anchored HDL-binding protein 1; LMF1, gene encoding lipase maturation factor 1; NGS, next generation sequencing; TG triglycerides

Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67

Management of acute pancreatitis

- Complete fasting in the first few day
- Hydration and analgesia
- In diabetes patients, intravenous insulin
- Manage secondary causes

Plasmapheresis or plasma exchange is generally not recommended

Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67

New and emerging treatments

- LPL gene therapy (alipogene tiparvovec): development suspended
- anti-APOC3 antisense (volanesorsen; AKCEA-APOCIII-LRx): approved in Europe
- anti-ANGPTL3 therapies (evinacumab; IONIS-ANGPTL3-LRx)

Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67

Dysbetalipoproteinaemia (formerly broad beta disease or hyperlipoproteinaemia type 3)

Affects 1 to 2 in 20000 people

Mode of inheritance is complex

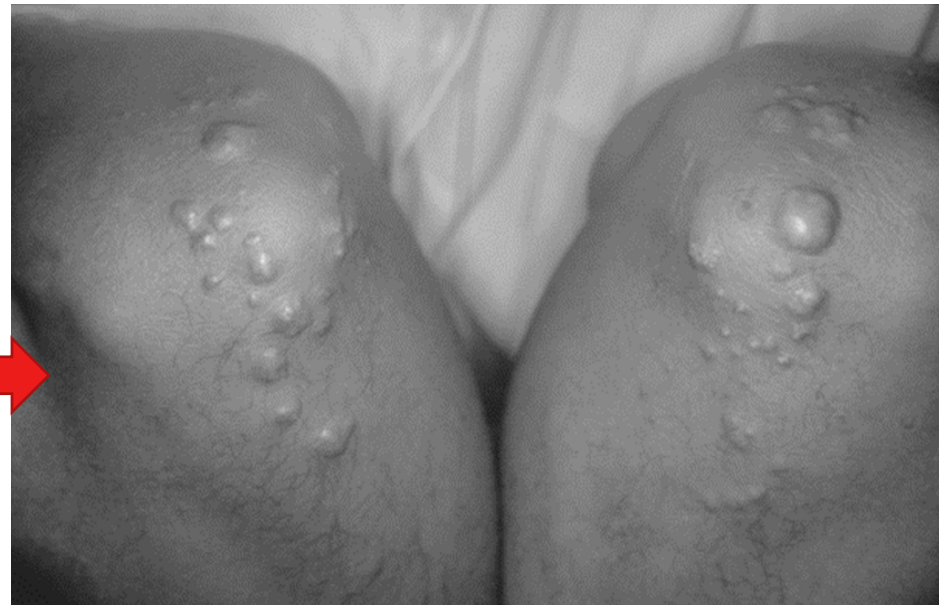
- Most cases are homozygous for the *APOE* E2 isoform
- About 10% have a large-effect dominant rare missense variant in *APOE*
- Polygenic susceptibility factors (e.g. insulin resistance or diabetes) and non-genetic factors (e.g. exogenous hormones, poor diet, hypothyroidism, renal disease, paraproteinaemia or systemic lupus erythematosus) also involved.

Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67

Dysbetalipoproteinaemia: clinical presentation

- Cholesterol and triglycerides are both elevated
- Differentiated from mixed dyslipidaemia by a low ratio of apolipoprotein B:total cholesterol
- Palmar and tuberoeruptive xanthomas on the elbows and knees
- Risk of premature coronary disease, especially peripheral arterial disease

Tuberous xanthomas on the knees



Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67
Photo courtesy Prof. Henry Ginsberg

Dysbetalipoproteinaemia: Treatment

Diet

- Limit alcohol intake
- Weight loss
- Diet fat restriction

Control of secondary factors

- Hypothyroidism
- Obesity, insulin resistance and diabetes

Fibrate therapy ± statin

Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67

HDL-related disorders

Hypoalphalipoproteinaemia: Very low HDL-C levels

First steps: exclude secondary causes of low HDL-C

	Very low HDL-C (<5th percentile)	**Moderately low HDL-C (<normal laboratory range)**
Underlying disease	• Severe hypertriglyceridaemia • Uncontrolled diabetes • Liver failure • Systemic / acute inflammation • Haemato-oncological diseases	• Moderate hypertriglycaemia • Type 2 diabetes • Obesity • Chronic inflammation • Growth hormone excess • Hypercortisolism • Chronic kidney disease
Lifestyle, drugs	• Androgens • Probucol	• Smoking • Physical inactivity • Thiazide-diuretics • Some beta-blockers • Anti-retroviral drugs

Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67

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Hypoalphalipoproteinaemia (very low HDL-C): Modes of inheritance

Disorder	Inheritance	Gene name	Chromosome
Tangier disease	ACD	ABCA1	9q31
Apo A-I deficiency	ACD	APOA1	11q23
LCAT deficiency; Fish eye disease	ACD	LCAT	16q22
ACD: autosomal codominant (i.e. heterozygotes express an abnormal phenotype about half as extreme as homozygotes)			

Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67

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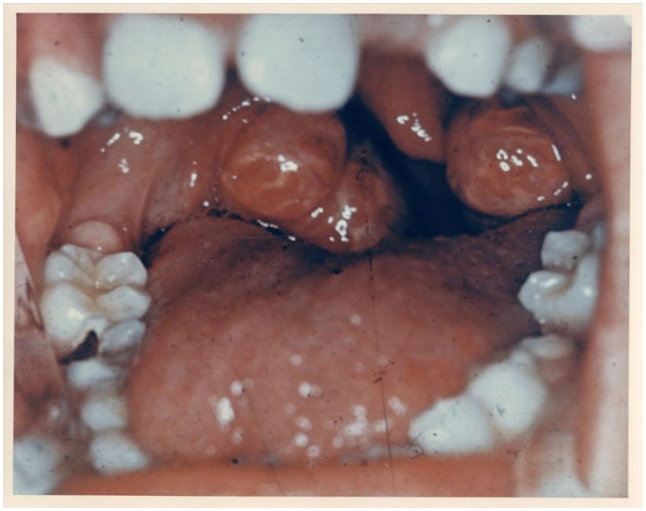
Prevalence of APOA1, ABCA1 and LCAT mutations (heterozygous carriers)

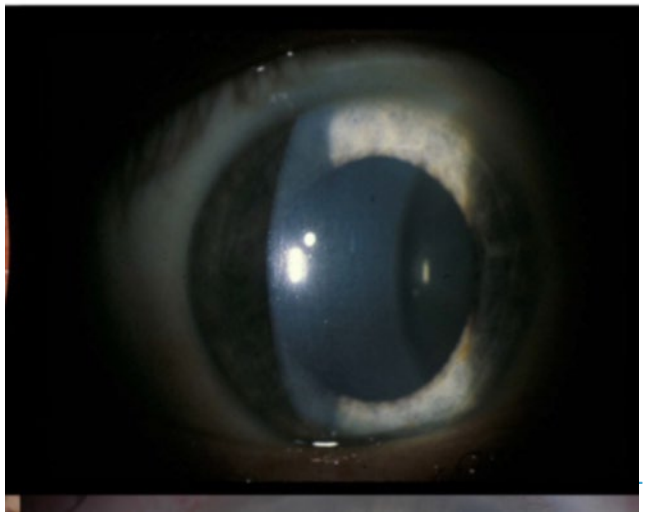
Gene	Protein	Number of mutations reported	Prevalence in general population
ABCA1	ATP-binding cassette transporter ABCA1	>170	~3 in 1000
APOA1	Apolipoprotein A-I	>60	~2.7 in 1000
LCAT	Lecithin–cholesterol acyltransferase	>80	Not known

Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67

Tangier disease

- Definitive diagnosis: two mutations in the *ABCA1* gene (either homozygous or compound heterozygous)
- Clinical presentation variable: common clinical signs include **enlarged yellowish tonsils**, peripheral neuropathy, splenomegaly, hepatomegaly and **corneal opacities**
- Laboratory findings: low platelet count, anaemia with acanthocytosis, moderate hypertriglyceridaemia, low LDL-C





Slit lamp examination of cornea

Ravesloot et al. Int J Ped Otorhinolaryngology 2014;78: 2305–7;
Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67

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Is Tangier disease associated with increased ASCVD risk?

- Low HDL-C
- Markedly reduced apoA-I mediated cholesterol efflux

BUT

- Conflicting reports in younger (40's) versus older (60's) cases
- Confounding due to broad age distribution and referral bias

Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67

Apolipoprotein A-I deficiency

Heterozygotes

- Although asymptomatic, ultrarare missense mutations are the second most frequent cause of familial amyloidosis

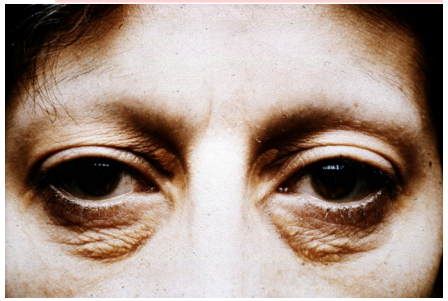
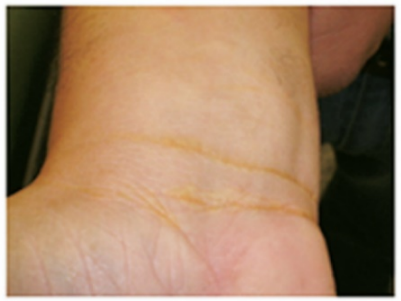
Homozygotes or compound heterozygotes

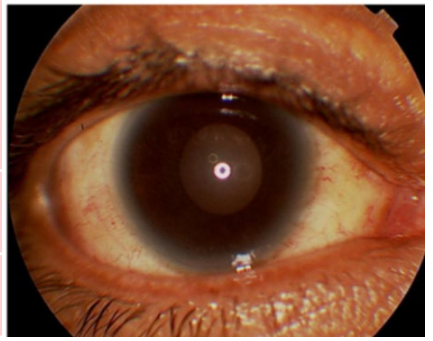
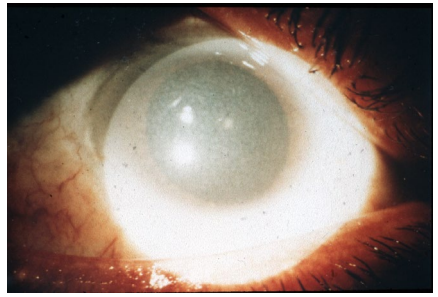
- <20 cases: almost complete HDL-C deficiency (<0.3 mmol/L or 10 mg/dL) and apo A-I <0.1 g/L
- Definitive diagnosis: targeted sequencing of the *APOA1* gene
- Associated with premature coronary heart disease

Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67

Clinical features of apolipoprotein A-I deficiency

	Two null APOA1 alleles	**Missense mutations and structurally abnormal apoA-I**
Clinical presentation	Xanthomas (eyelids or covering the body)	Corneal clouding
Premature CHD	Yes	?
HDL-C	Not measurable	Not measurable
Apo A-I	Undetectable	Detectable: 1-5 mg/dL

Römling et al. Arterioscler. Thromb 1994:14:1915-22; Santos et al J Clin Lipidol 2008;2:237–47; Miccoli et al. Circulation 1996;94:1622-8; Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67

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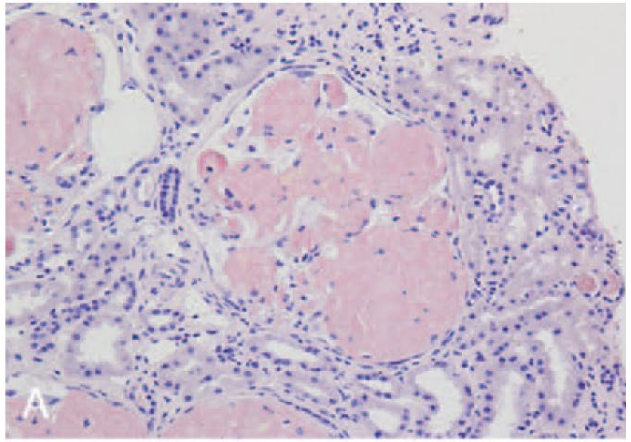
APOAI variants associated with amyloidosis

- 20 variants, autosomal dominant
- Affected organs include kidney, liver, GI tract, peripheral nervous system, testes, ovary, uterus, larynx and skin
- Location of the structural alteration determines the site of deposition of apo A-I-amyloid
- mutations in the amino-terminal domain are mainly associated with hepatic and renal amyloidosis
- mutations in residues from 173 to 178 are mostly responsible for cardiac, laryngeal, and cutaneous amyloidosis



Renal apoA-I-related amyloidosis dyed with Congo red

Lu et al. Medicine 2017;96:39(e8148);
Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67

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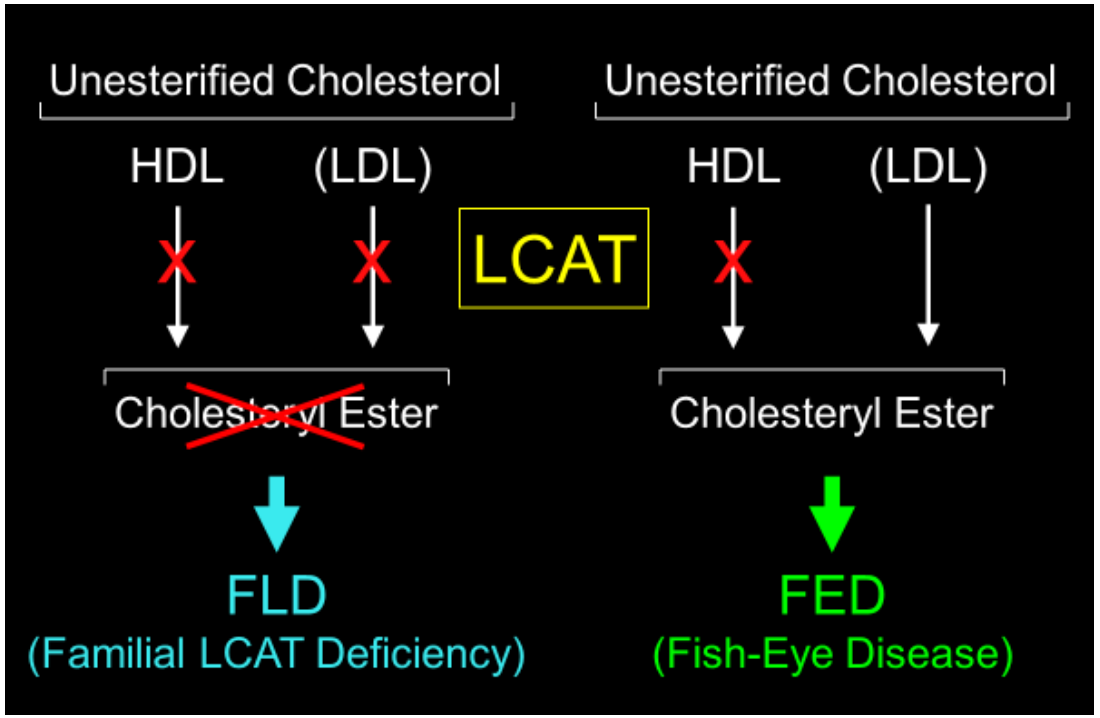
LCAT deficiency syndromes: Familial LCAT deficiency (FLD) and Fish eye disease (FED)

- >65 mutations, population prevalence is not known
- Both FLD and FED are characterised by very low plasma HDL-C levels, with low LDL-C and apoB
- Definitive diagnosis is by DNA sequencing demonstration of two LCAT gene mutations



Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67

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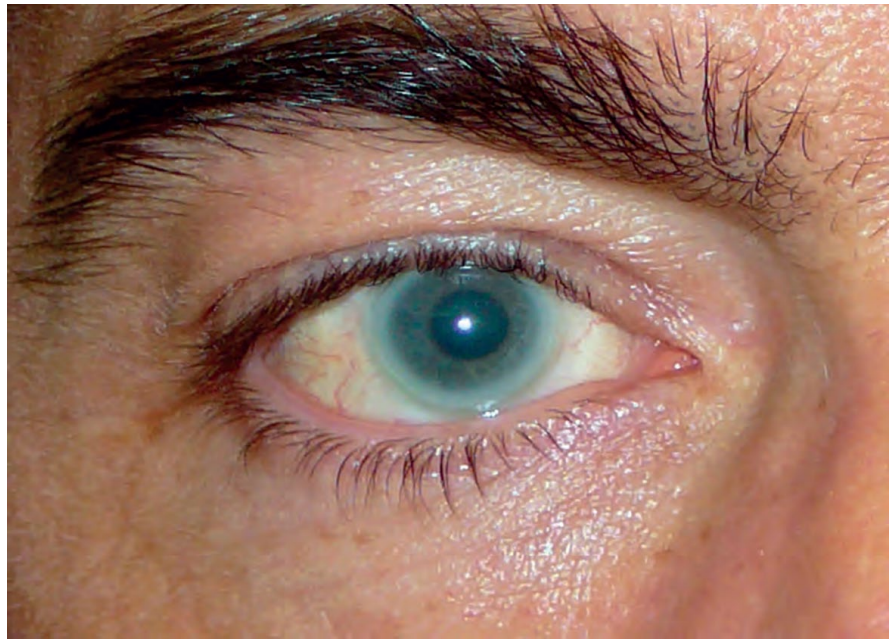
Familial LCAT deficiency (FLD): Clinical presentation

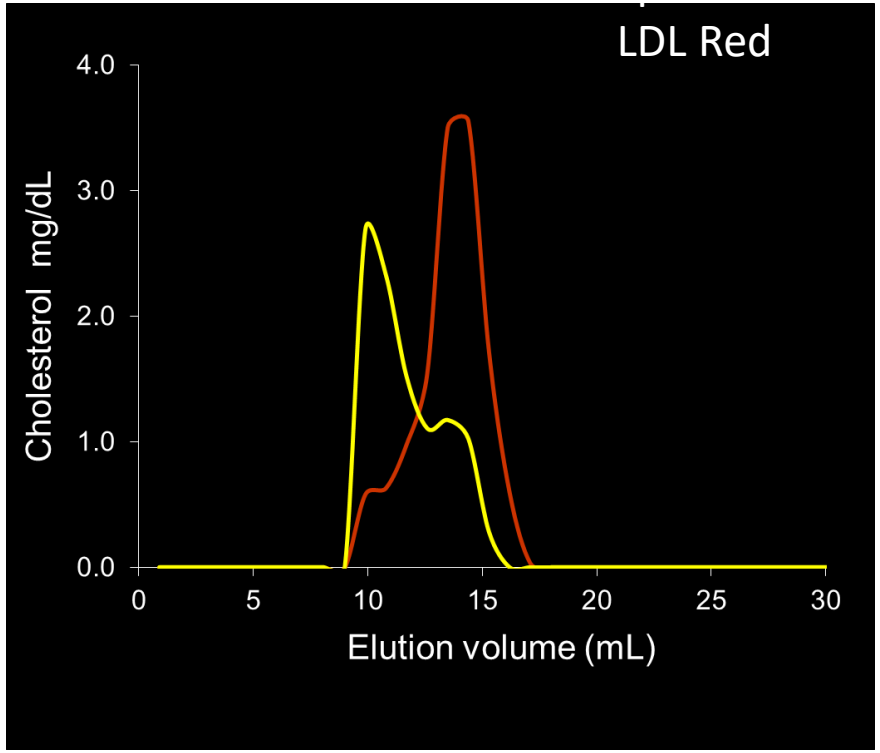
- Corneal opacity
- Anaemia (increased reticulocyte count)
- Renal disease
- ?Premature CHD



Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67;
Photo courtesy of Prof. Laura Calabresi

Renal disease in FLD

- Major cause of morbidity and mortality
- Proteinuria often detected in the early 20's
- Renal failure develops in the 40's-50's
- Lipid deposition and thickening of glomerular basement membrane



Lipoprotein X (LpX), an abnormal cholesterol-rich particle, is a feature of FLD. As a result of plasma accumulation, LpX becomes trapped in renal capillaries, inducing endothelial damage and vascular injury.

Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67
Ossoli A et al. PLoS ONE 2016; 11(2): e0150083.

Management of rare low HDL-C syndromes

Syndrome	Management
ApoA-I deficiency **Tangier disease**	No specific treatment Optimal control of other risk factors to manage ASCVD risk **Novel:** synthetic apoA-I infusion
LCAT deficiency syndromes (FLD, LED)	No specific treatment ACE inhibitors/angiotensin receptor blockers for renal disease Corneal transplantation (to restore vision) **Novel:** enzyme replacement therapy with human recombinant LCAT and small molecules enhancing LCAT activity

Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67

HDL-related disorders

Hyperalphalipoproteinaemia: Very high HDL-C levels

Hyperalphalipoproteinaemia (very high HDL-C): Modes of inheritance

Disorder	Inheritance	Gene name	Chromosome
Cholesteryl ester transfer protein deficiency	ACD	CETP	16q13
Scavenger receptor B1 deficiency	ACD	SCARB1	12q24
Hepatic lipase deficiency	ACD	LIPC	15q21
ACD: autosomal codominant (i.e. heterozygotes express an abnormal phenotype about half as extreme as homozygotes)			

Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67

Rare high HDL-C syndromes

Loss-of-function mutations in *CETP* and *SRB1* genes

- Plasma HDL-C levels >2.6 mmol/L (100 mg/dL)
- Clinical phenotype and association with ASCVD poorly defined

Hepatic lipase deficiency: loss-of-function mutations in *LIPC* gene

- Elevated abnormal plasma HDL-C together with high cholesterol and triglycerides
- May be increased risk of ASCVD

Currently, there are no investigational treatments

Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67

Unmet needs in managing rare lipoprotein disorders

- Practical issues: cost and access to diagnostic modalities and emerging therapies
- Lack of information about these disorders
- Lack of effective treatments
- Lack of hard outcomes data, due to logical constraints

There is an urgent need for collaborative registries with integration of genomic technologies to improve awareness, management, and access to effective therapy

Hegele RA et al. Lancet Diabetes Endocrinol 2020;8:50-67

Websites

- National Organization for Rare Diseases; https://rarediseases.org/
- National Institutes of Health Genetics Home Reference; https://ghr.nlm.nih.gov/condition
- Rare Disease Report; https://www.mdmag.com/specialty/rare-diseases
- Orphanet; https://www.orpha.net/consor/cgi-bin/index.php?lng=EN
- Hypercholesterolemia Foundation; https://thefhfoundation.org/
- FH Canada; https://www.fhcanada.net/
- Heart UK; https://www.heartuk.org.uk/

About the EAS Task Force

This EAS Task Force was convened in June 2018 and led by Professor Alberico L. Catapano, University of Milan and IRCCS MultiMedica, Milan, Italy and Professor Henry N. Ginsberg, Columbia University, New York, USA.

Logistic support for travel to attend two Task Force meetings was provided by the EAS. There were no other sources of funding.

For individual expert disclosures refer to the Task Force statement

https://www.eas-society.org/page/consensus_papers

The Mission of the EAS

The EAS was founded in 1964 with the mission to “advance and exchange knowledge concerning the causes, natural history, treatment and prevention of atherosclerotic disease”.

With atherosclerosis becoming an increasingly important concern as European populations grow older, the work of the Society is today more relevant than ever.

For further information: https://www.eas-society.org/