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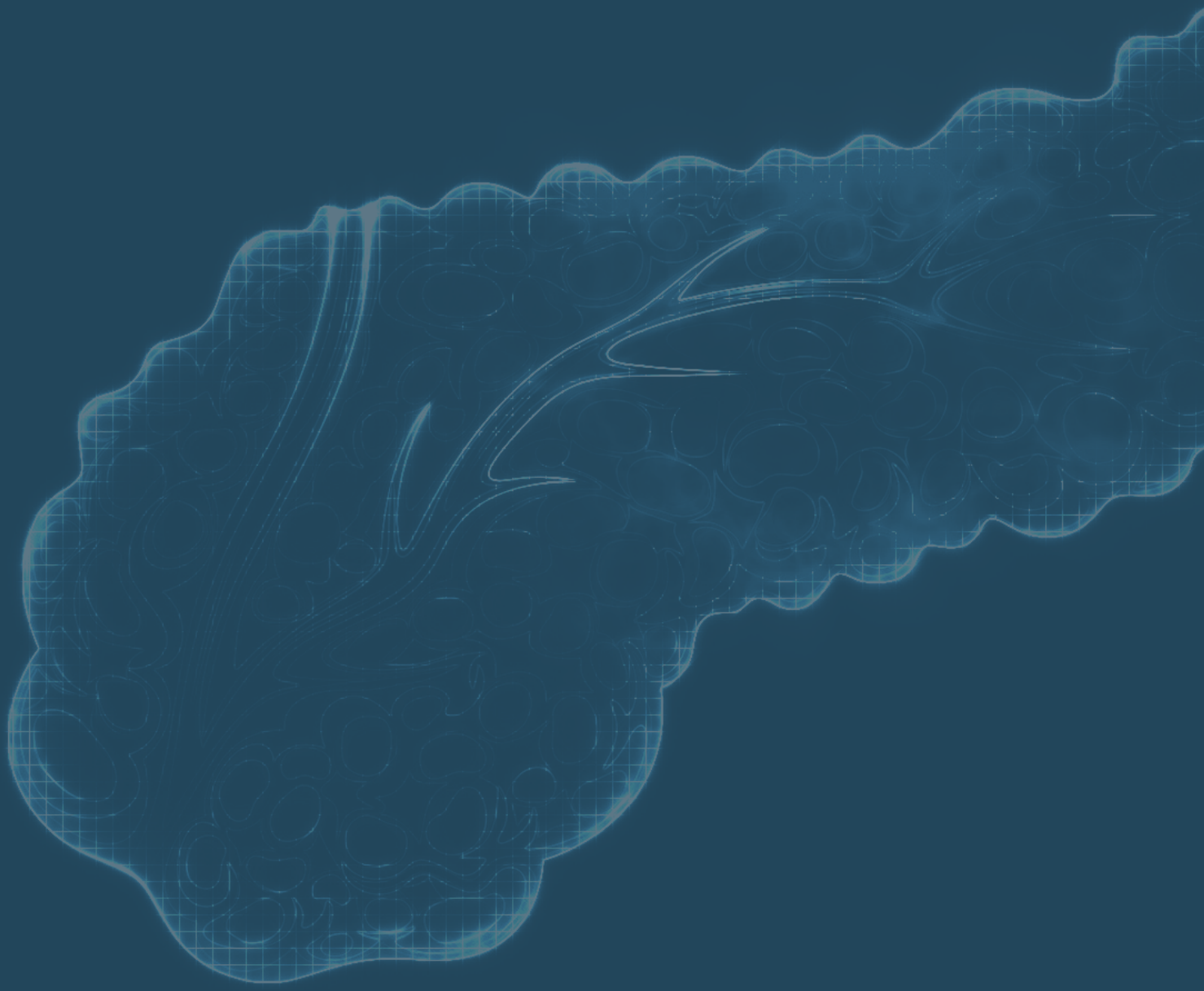


Severe hypertriglyceridemia:

Using genetics for diagnosis

Step by step to diagnosis

FCS diagnosis is based on a four-step approach:

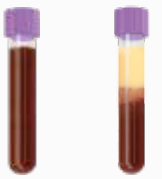
1. **Suspected** hypertriglyceridemia
2. **Verification** of the suspicion
3. **Confirmation** of the suspicion by using genetic testing
4. **Distinction between** monogentic vs. polygenic hypertriglyceridemia

1 **Suspected** hypertriglyceridemia

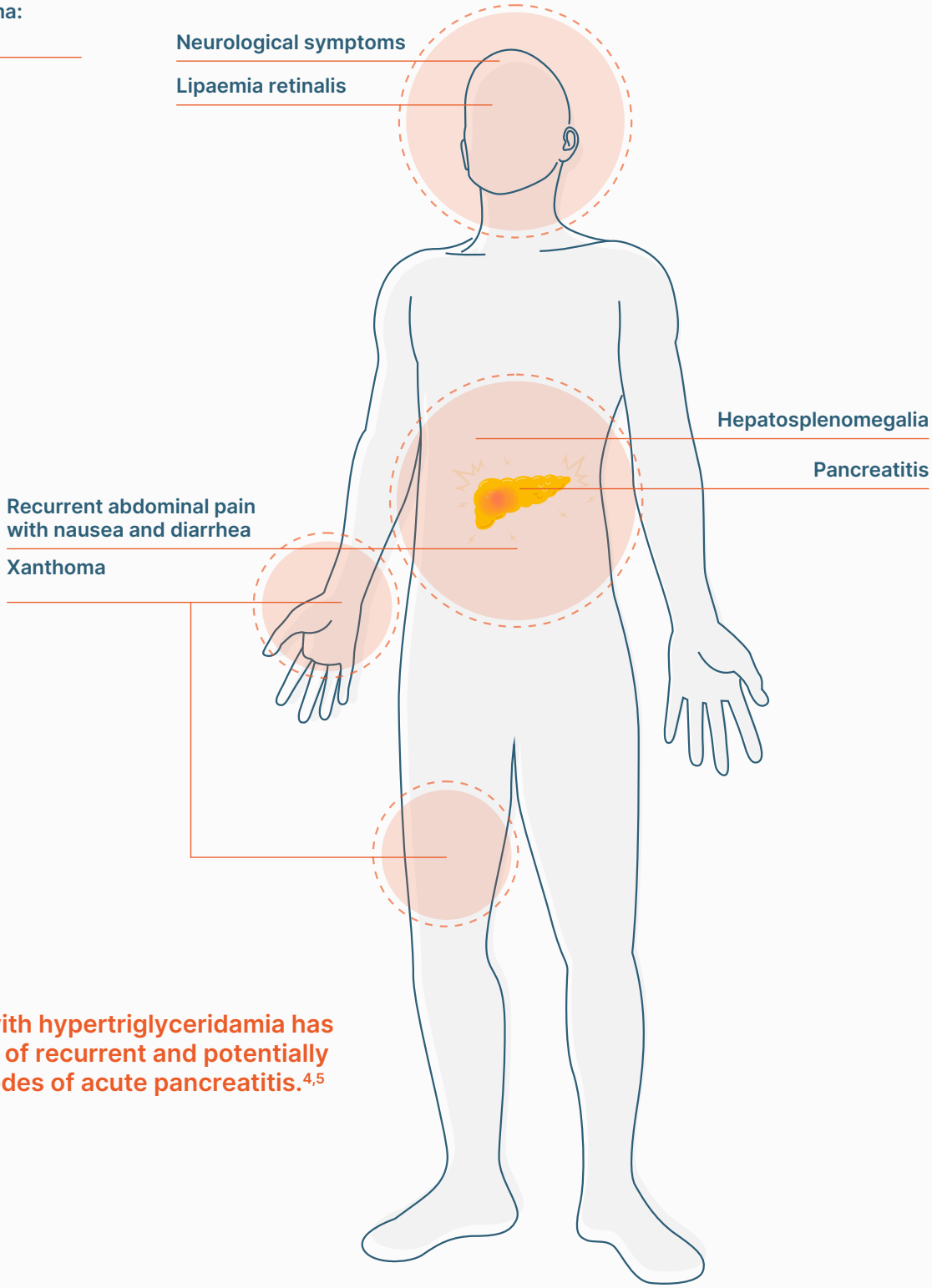
Moderate:[1] triglycerides (TG) 200-885 mg/dl (2-9,9 mmol/l)
Severe:[1] triglycerides (TG) >885 mg/dl (>10 mmol/l)

Severe hypertriglyceridemia/chylomicronemia can lead to the following symptoms:[2,3]

Lipemic blood plasma:
Refrigerator test



Before After



Patients with hypertriglyceridamia has a high risk of recurrent and potentially fatal episodes of acute pancreatitis.[4,5]

2 **Verification** of the suspicion

Basic diagnostics for suspected lipid metabolism disorders:[6]

- Triglycerides total
- Cholesterol HDL
- Cholesterol
- Non-HDL cholesterol
- LDL cholesterol
- Lipoprotein (a) (at least once), especially in diabetes mellitus, metabolic syndrome
- Apolipoprotein B

TG > 400 mg/dl (4.5 mmol/l): Additional lipid electrophoresis[6]
TG > 885 mg/dl (10 mmol/l): Diagnosis score for familial chylomicronemia syndrome (FCS score):[7]

1. Fasting TG levels >885mg/dl or 10 mmol/L for 3 consecutive blood analyses
   Fasting TG > 1,750 mg/dl (20 mmol/l)) at least once (+1)
2. Previous TG < 175 mg/dl (< 2 mmol/dl) (-5)
3. no secondary factors[b] (except pregnancy[c] and ethinylestradiol)(+2)
4. History of pancreatitis (+1)
5. unexplained recurrent abdominal pain (+1)
6. no history of familial combined hyperlipidemia (+1)
7. No response (TG decrease < 20 %) to lipid-lowering therapy (+1)
8. Onset of symptoms at the age of
   < 40 years (+1)
   < 20 years (+2)
   < 10 years (+3)

FCS score:
≥ 10: FCS very likely
≤ 9: FCS unlikely
< 8: FCS very unlikely

”FCS score” > 7 points; consider genetic testing[8]

3 **Confirmation** of the suspicion by using genetic testing

Important genes and proteins in the metabolism of TG-rich lipoproteins[9]

Protein	Functions and regulation	In case of defect/deficiency or inhibition
Degradation proteins and cofactors (deficiency leads to an increase in TG-rich proteins)		
Lipoprotein lipase (LPL)[10-16]	• Hydrolysis of triglycerides in chylomicrons and VLDL and peripheral uptake of FFS • is activated by APO A5 and APO C2 • is inhibited by APO C1, APO C3 and ANGPTL 3, 4 and 8	• Severe monogenic HTG with chylomicronemia and elevated VLDL • Increased risk of acute pancreatitis • Early manifestation in infancy and childhood
Glycosyl-Phosphatidyl-Inositol cored High density Lipoprotein Binding Protein (GPIHBP1)[16-21]	• Endothelial LPL transport protein • stabilizes the binding of chylomicrons • supports lipolysis	• Severe monogenic HTG with chylomicronemia • Late manifestation due to autoantibodies possible in adulthood
Apolipoprotein C2 (APO C2)[10, 22]	• Cofactor of the LPL • activates LPL	• Severe monogenic HTG with chylomicronemia and elevated VLDL • Early manifestation in infancy and childhood
Apolipoprotein A5 (APO A5)[23, 24]	• Cofactor of the LPL • Amplifier of the LPL activity	• Severe monogenic HTG with chylomicronemia
Lipase Maturation Factor - 1 (LMF1)[25, 26]	• Chaperone, mediates folding of LPL in adipocytes and myocytes	• Severe monogenic HTG with chylomicronemia
Glycerol-3-phosphate dehydrogenase 1 (GPD-1)[27]	• Degradation of glycerol-3-phosphate, the starting product of TG synthesis	• Severe monogenic HTG due to increased TG synthesis
Hepatic lipase (HL)[28]	• Hydrolysis of triglycerides, phospholipids • Conversions from VLDL to LDL and from large HDL to small HDL	• Mixed hyperlipidemia • Accumulation of remnants
Apolipoprotein E (APO E)[29, 30]	• Ligand for the LDL receptor and LRP-1 • activates LCAT • Lipid transport in the brain • Support of LDL-mediated uptake and elimination of chylomicron remnants	• Hypertriglyceridemia (dysbetalipoproteinemia) • Increased risk of Alzheimer's disease (APO E4 variant)
CAMP Responsive Element Binding Protein-3-Like-3 (CREB3L3)[31, 32]	• Transcription factor in the liver that regulatestriglycerides and cholesterol	• Severe hypertriglyceridemia
Glucokinase regulatory protein (GCKR)[31, 33]	• Regulation of the activity of the enzyme glucokinase in the liver	• Severe hypertriglyceridemia

4 Distinction between monogentic vs. polygenic hypertriglyceridemia

Monogenic and polygenic forms of severe hypertriglyceridemia

	Monogenic HTG	Polygenic HTG
Degradation proteins and cofactors (deficiency leads to an increase in TG-rich proteins)		
Former designations	Familial chylomicronemia, hyperlipoproteinemia type 1 (WHO)	Mixed dyslipidemia, hyperlipoproteinemia type 5 (WHO)
Main lipoprotein disorder	Variable increase in TG-rich lipoproteins: Chylomicrons, VLDL, chylomicron remnants and VLDL remnants	
Ass. Lipoprotein disorders	Reduction of LDL and HDL	
Typical start	Childhood or adolescence	Adulthood
Clinical features	• early recurrent pancreatitis • Failure to thrive • Abdominal pain • Nausea • Vomiting • Eruptive xanthomas • Lipaemia retinalis • Hepatosplenomegaly	• Abdominal pain • Nausea • Vomiting • Eruptive xanthomas (rarer) • Lipaemia retinalis (rarer) • Pancreatitis (~1% risk per year)
Cardiovascular risk	Only slightly increased	Some indications of increased risk
Prevalence rate	Rare, ~1:100,000 to ~1:1,000,000	Frequent, ~1:600
Influence of non-genetic factors on the phenotype	Low	High
Inheritance pattern	Autosomal recessive, occasionally autosomal co-dominant	Familial clustering, but no classic Mendelian inheritance
Genetic causes	• Mutations in LPL, APO A5, APO C2, CREB3L3, GCKR, GPD-1[27], GPIHBP1, LMF-1. • Others could be identified in the future.	• Heterozygous rare variants in LPL, APO A5, • APO B, APO C2, APO C3, APO E, CREBH, • GCKR, GPD-1, GPIHBP1 and LMF-1 with large phenotypic effects • Common variants (genetic polymorphisms, SNPs*) with small effects in ~40 genes identified in genome-wide association studies
Therapy goal	• Prevention of recurrent pancreatitis and its consequences.	• Prevention of recurrent pancreatitis and its consequences • Reduction of the cardiovascular risk

Table modified and supplemented according to Brahm (2015)[9]
* SNPs = single nucleotide polymorphism = susceptibility variants = polymorphisms

Genetic causes of HTG[7, 32, 34]

Influencing factors	Gene	Inheritance pattern	Possible diagnosis
Constant heavy HTG	LPL, APO A5, APO C2, CREB3L3, GCKR, GPD-1, GPIHBP1, LMF-1:	Homozygous mutation Combined heterozygous mutation Heterozygous co-dominant mutation	**Monogenic HTG, also known as familial chylomicronemia syndrome:** The genetic load is high enough to cause constant HTG, regardless of other factors such as additional mutations or lifestyle factors.
Non-genetic factors*	LPL, APO A5, APO C2, APO C3, APO E, CREB3L3, GCKR, GPD-1, GPIHBP1, LMF-1:	**Heterozygous** mutation with major metabolic effects **+ SNPs**** **Combination of common SNPs** or genetic polymorphisms** with small effects in ~40 genes Sporadic severe HTG	**Polygenic HTG, also known as multifactorial chylomicronemia syndrome:**[9,32,34] A single mutation is not sufficient to cause a clinical phenotype. The severity of HTG is determined by cumulative/interactive effects of several genetic risk variants.***

* Lifestyle factors, medication and concomitant diseases; ** SNPs = single nucleotide polymorphism = susceptibility variants = polymorphisms

*** These risk variants include both heterozygous rare variants with major metabolic effects and common variants polymorphisms) with minor effects.
These mutations occur in combination with TG-increasing SNPs. A large number of SNPs with an effect on TG can also lead to polygenic HTG on their own.

Term	Definition
Homozygous Mutation	A genetic condition where an individual has two copies of the same mutated gene, one inherited from each parent.
Combined Homozygous Mutation	This occurs when an individual has two different mutations, one on each copy of gene, inherited from each parent.
Heterozygous Co-dominant Mutation	A situation where two different alleles (versions of a gene) are present, and both contribute to the phenotype.
Heterozygous Mutation with major Metaboic Effects+SNPs	A single allele mutation that has a significant impact on metabolism, often combined with single nucleotide polymorphisms (SNPs) that can either exacerbate or mitigate the metabolic effects.
Combination of Common SNPs or Genetic Polymorphisms with small Effects	Multiple SNPs or genetic variations that each have a small effect on their own, but whe combined, can have a significant impact on a trait or condition.

Therapeutic approach for patients with severe HTG[1, 35]

Triglycerides < 10 mmol/l (885 mg/dl)

Primary goal:

cardiovascular risk reduction

- Depending on the overall risk, consider further reduction of non-HDL-C
- Consider further LDL-C reduction

Triglycerides ≥ 10 mmol/l (885 mg/dl)

Primary goal:

prevention of pancreatitis

- TG reduction < 10 mmol/l (885 mg/dl) or below the individual pancreatitis threshold
- Involve lipidologists

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List of abbreviations

ANGPTL3, angiopoietin-like 3 protein; ANGPTL4, angiopoietin-like 4 protein; ANGPTL8, angiopoietin-like 8 protein; APO A5, apolipoprotein A5; APO C2, apolipoprotein C2; APO E, apolipoprotein E; C, cholesterol; CREBH, cyclic adenosine monophosphate (cAMP)-responsive element-binding protein H cyclic adenosine monophosphate (cAMP)-responsive element-binding protein H); CREB3L3, CAMP-Responsive Element-Binding Protein-3-Like-3; FCS, familial chylomicronemia syndrome; FFS, free fatty acids; GKCR, glucokinase regulatory protein; HDL, high density lipoprotein; GKCR, glucokinase regulatory protein; HDL, high density lipoprotein. high density lipoprotein; LCAT, lecithin-cholesterol acyltransferase; LDL, low density lipoproteins; LPL, lipoprotein lipase; LRP1, low density lipoprotein receptor-related protein 1; TG, triglycerides; VLDL, very low density lipoprotein; WHO, World Health Organization

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