# Primary Hypertriglyceridemia

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## Introduction

Hypertriglyceridemia (HTG) is often defined by plasma triglyceride (TG) concentration >95th percentile for age and sex. Patients with HTG frequently have concomitant comorbidities such as poor diet, alcohol use, obesity, metabolic syndrome, and type 2 diabetes [1–3]. HTG can be further classified as being of either primary type, in which there is an identified or presumed familial or molecular genetic basis for the condition, or secondary type, in which one of several secondary factors contributes to disease expression [1, 3]. Genetic factors can influence the severity of the plasma TG elevation in the presence of a secondary factor [4]. This chapter focuses on primary HTG, both the rare monogenic and common polygenic forms of HTG, in addition to clinical considerations and treatment.

## "Familial" Does Not Mean Monogenic

An important concept that has emerged in the past few years is that while most cases of primary HTG are familial in nature, only a minority is truly monogenic (typically autosomal recessive) [3–6]. In the pregenomic era, primary HTG disorders were presumed mostly to be monogenic, by analogy with and extrapolation from other archetypal monogenic lipid disorders, such as familial hypercholesterolemia (FH). But while FH results from single strong-effect mutations in genes that perturb low-density lipoprotein (LDL) receptor function and show cosegregation with high LDL cholesterol concentrations in families, most cases of "familial" HTG are polygenic rather than monogenic disorders [2–6]. While HTG clusters in families, it usually does not follow classical Mendelian patterns of inheritance, and inconsistently shows vertical transmission in family pedigrees. But despite this, the idea that most HTG states are monogenic has persisted in the literature and textbooks over decades, likely because the term "familial" is included in the names of several classical primary HTG disorders. However, it is generally incorrect to conflate a "familial" disorder with a "monogenic" disorder: While many cases of HTG are familial, they are usually not monogenic [4–6].

## Clinical Diagnosis of HTG

HTG is usually diagnosed when fasting plasma TG concentration exceeds a threshold value, such as the 95th percentile when adjusted for age and sex. The 95th percentile for TG corresponds to ∼3.0–3.4 mmol/L (∼250–300 mg/dL) for most North American adults. Severe HTG is

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**Table 11.1** Hypertriglyceridemia (HTG): proposed clinical definitions

| General definition (ref. 1) | | ATP guidelines (ref. 2) | | Endocrine society (ref. 3) | |
|---|---|---|---|---|---|
| Category | Serum TG (mmol/L) | Category | Serum TG (mmol/L) | Category | Serum TG (mmol/L) |
| Normal | <3 | Normal | <1.7 | Normal | <1.7 |
| Hypertriglyceridemia | >3–3.4 (>95th percentile) | Borderline high | 1.7–2.3 | Mild | 1.7–2.3 |
| | | | | Moderate | 2.3–11.2 |
| Severe hypertriglyceridemia | >10 | High | 2.3–5.6 | Severe | 11.2–22.4 |
| | | Very high | >5.6 | Very severe | >22.4 |

*TG* triglyceride, *ATP* Adult Treatment Panel III of the National Cholesterol Education Program

**Table 11.2** Types of hypertriglyceridemia (HTG)

| Name | Primary lipoprotein abnormality | Lipid profile | Population prevalence |
|---|---|---|---|
| Familial chylomicronemia (formerly HLP type 1) | Elevated chylomicrons | ↑↑↑TG ↑TC | 1 in 1 million |
| Combined hyperlipidemia (formerly HLP type 2B) | Elevated VLDL, elevated LDL | ↑↑TG ↑↑TC | 1 in 40 |
| Dysbetalipoproteinemia (formerly HLP type 3) | Elevated IDL, elevated chylomicron remnants | ↑↑TG ↑↑TC | 1 in 10,000 |
| Primary simple hypertriglyceridemia (formerly HLP type 4) | Elevated VLDL | ↑↑TG ↑TC | 1 in 20 |
| Primary mixed hyperlipidemia (formerly HLP type 5) | Elevated chylomicrons, elevated VLDL | ↑↑↑TG ↑↑↑TC | 1 in 600 |

Abbreviations: as in Table 11.1 plus

*HLP* hyperlipoproteinemia, *TC* total cholesterol, *VLDL* very low-density lipoprotein, *LDL* low-density lipoprotein, *IDL* intermediate density lipoprotein, *TG* triglyceride

often defined when fasting plasma TG concentration >10 mmol/L (>900 mg/dL) [1–3]. Proposed definitions vary however (Table 11.1). For instance, the Adult Treatment Panel III guidelines of the National Cholesterol Education Program has suggested a classification system with four discrete categories: normal fasting TG is <1.7 mmol/L (<150 mg/dL), borderline high TG is 1.7–2.3 mmol/L (150–199 mg/dL), high TG is 2.3–5.6 mmol/L (200–499 mg/dL), and very high TG is >5.6 mmol/L (>500 mg/dL) [2]. The Endocrine Society has proposed another system with five clinical strata: normal TG is <1.7 mmol/L (<150 mg/dL), mild HTG is 1.7–2.3 mmol/L (150–199 mg/dL), moderate HTG is 2.3–11.2 mmol/L (200–999 mg/dL), severe HTG is 11.2–22.4 mmol/L (1000–1999 mg/dL), and very severe HTG is >22.4 mmol/L (>2000 mg/dL) [3]. Other schemes have been proposed, but no scheme predominates in clinical use.

## Classification of HTG Phenotypes

Phenotypic heterogeneity among HTG patients is defined by qualitative and quantitative biochemical differences in plasma lipoproteins. In the pregenomic era, a commonly used classification scheme—the Fredrickson or World Health Organization (WHO) International Classification of Diseases (ICD) hyperlipoproteinemia (HLP) phenotypes—was based on patterns of lipoprotein fractions (summarized in Table 11.2). Five of the six WHO ICD phenotypes include HTG in their definitions [7, 8]. The exception is FH (HLP type 2A), which most often results from mutations in *LDLR* encoding the LDL receptor [8]. The HLP phenotypes defined by HTG include one monogenic pediatric phenotype called familial chylomicronemia (HLP type 1), and four polygenic "familial" phenotypes, called combined hyperlipidemia (HLP type 2B), dysbetali-

poproteinemia (HLP type 3), simple HTG (HLP type 4), and mixed hyperlipidemia (HLP type 5).

Sub-phenotypes of HTG are defined by the specific class or classes of TG-rich lipoprotein particles that accumulate in plasma, including chylomicrons, very-low density lipoprotein (VLDL), or intermediate-density lipoprotein (IDL) [8]. Frequently, the excess of TG-rich lipoproteins coexists with other lipoprotein disturbances. For instance, HLP type 4 is characterized by elevated VLDL concentrations in isolation. HLP type 5 is characterized by elevations in both chylomicron and VLDL concentrations. HLP type 3 is characterized by elevated IDL concentrations. Finally, HLP type 2B is characterized by elevated VLDL and LDL concentrations. Decreased high-density lipoprotein (HDL) cholesterol is very commonly seen in patients with all types of HTG. Implicit in this classification system was the idea that the differences between the HTG-associated phenotypes were due to differences at the molecular genetic level [8], however recent data suggest that this is often not the case [4–8]. We believe that continued use of this traditional nomenclature, while familiar to older clinicians, may be retrogressive. We endeavor in this chapter to refer to this terminology as "formerly known as," where possible.

## Secondary Factors Contributing to HTG

Secondary factors that are associated with HTG are discussed in depth elsewhere [3], but include: obesity, metabolic syndrome (where TG concentration $\geq 1.7$ mmol/L [$\geq 150$ mg/dL] is part of the diagnosis), diet with high-positive energy-intake balance and high fat or high glycemic index, alcohol consumption, diabetes (particularly type 2), renal disease (particularly uremia or glomerulonephritis), pregnancy (particularly in the third trimester), autoimmune disorders such as paraproteinemia or systemic lupus erythematosus, and several types of medications, including corticosteroids, oral estrogen, tamoxifen, thiazides, non-cardioselective beta-blockers, bile acid sequestrants, cyclophosphamide, antiretroviral regimens, phenothiazines, and second-generation antipsychotic agents.

## Monogenic HTG: Familial Chylomicronemia (Formerly Known as HLP Type 1)

As mentioned above, only one type of HTG is truly monogenic, namely familial chylomicronemia, also known at chylomicronemia syndrome or HLP type 1, which is characterized by the pathological presence of chylomicrons in the blood after a fasting period of 12–14 h [1–3].

*Epidemiology* Familial chylomicronemia is an extremely rare disorder with an estimated overall prevalence in the population of approximately one in 1 million [1–3].

*Clinical Features* Familial chylomicronemia usually presents during infancy or childhood, and generally by adolescence [1, 9, 10]. Clinical features include failure to thrive, eruptive xanthomas over extensor surfaces and buttocks, lipemia retinalis, hepatosplenomegaly, recurrent abdominal pain with or without nausea and vomiting, and a strong predisposition for recurrent pancreatitis [9, 10]. Other rarer presentations that may be seen especially include intestinal bleeding, pallor, anemia, irritability, diarrhea, seizures, and encephalopathy; the underlying mechanisms for these uncommon associated symptoms are often unclear [9–11].

Xanthomas are characterized by raised crops of small yellowish papules surrounded by erythematous halos that appear most commonly on extensor surfaces of the extremities, the buttocks and the shoulders [12] (Fig. 11.1). Xanthomas tend to erupt concomitant with severe elevations in plasma TG levels, and gradually disappear over weeks to months as TG levels improve [13]. Microscopic examination of scrapings from xanthomas reveal the presence of lipid-containing macrophages or foam cells within the superficial reticular dermis, as well as infiltration with lymphocytes and neutrophils [12] (Fig. 11.1). The pathophysiology of xanthomas is thought

**Fig. 11.1** Clinical manifestations of primary hypertriglyceridemia (HTG). **a** Lipemic plasma. Whole blood has been allowed to stand at 4 °C overnight. The sample on the *left* comes from a patient with fasting total cholesterol and triglyceride (*TG*) of 14.2 and 41.8 mmol/L, respectively. The sample on the *right* comes from a normolipidemic subject. **b** Eruptive cutaneous xanthomas. Skin lesions filled with foam cells that appear as *yellow*, morbiliform eruptions between 2 and 5 mm in diameter often with erythematous areolae, which are most often associated with markedly elevated plasma chylomicrons in familial chylomicronemia (HLP type 1) or primary mixed dyslipidemia (HLP type 5) and usually occur in clusters on the trunk, buttock, or extremities. **c** Lipemia retinalis. A *milky* appearance of the retinal vessels and *pink* retina can be seen when plasma TG >35 mmol/L. **d** Tuberous xanthomas. Skin lesions filled with foam cells that appear as *reddish* or *orange*, and often shiny nodules up to 3 cm in diameter, which are usually moveable and nontender, usually on extensor surfaces, and are found in patients with familial dysbetalipoproteinemia (FDL; HLP type 3). **e** Palmar crease xanthomas. Skin lesions filled with foam cells that appear as *yellowish*, deposits within palmar creases, and are pathognomonic for FDL. (Figure from [1])

to be due to deposition of a large amount of lipid of chylomicron origin in the tissue, which overwhelms the clearance capacity of the macrophages, resulting in lipid accumulation [12]. This free lipid acts as a catalyst for the inflammation cascade that leads to the development of the eruptive xanthomas often seen in familial chylomicronemia patients [12].

Lipemia retinalis is the term used to describe retinal vessels that appear whitish-pink on fun-

doscopic (Fig. 11.1) examination due to the presence of chylomicron-rich serum [13]. This condition is a physical sign only and does not affect vision [13]. Hepatosplenomegaly is rapidly reversible with correction of serum TG levels [13].

Patients with familial chylomicronemia are at lifelong risk of developing recurrent acute pancreatitis [14]. This risk increases when TG >10 mmol/L (>900 mg/dL) and is greatest with TG levels >20 mmol/L (>1800 mg/dL) [15].

Pancreatitis is often serious and can be fatal. Besides the acute abdominal discomfort, severe chronic complications include the development of chronic pancreatitis, pancreatic insufficiency, pancreatic necrosis, pancreatic abscess, or pancreatic pseudocyst [10, 13]. The pathophysiology underlying HTG-induced pancreatitis is not entirely understood but is thought to be due to increased activity of pancreatic lipase-mediated hydrolysis of circulating or infiltrating TG into their component fatty acids in the pancreas [16]. These unbound fatty acids are thought to be toxic to the pancreatic acinar cells, leading to the premature activation of trypsinogen and autodigestion injury of the surrounding pancreatic tissue [16]. Increased levels of chylomicrons themselves are also thought to worsen the pathophysiology by causing capillary plugging and local ischemia [16].

Cardiovascular disease (CVD) risk is inconsistently associated with familial chylomicronemia. Earlier observations suggested that younger patients with chylomicronemia are less prone to CVD than are patients with other lipid disorders [17, 18]. Likewise, autopsy studies on this patient population failed to show any significant burden of atherosclerosis [18], presumably because chylomicrons are too large to penetrate the endothelial surface [18]. In addition, LDL cholesterol concentrations are lower than normal in patients with familial chylomicronemia [18].

Small prospective case studies have suggested that some patients with familial chylomicronemia can develop premature atherosclerosis, despite LDL cholesterol concentrations <1.6 mmol/L [18]. This was thought to be due to a pro-atherogenic effect of some smaller subspecies of chylomicron remnants, particularly after modifications such as oxidation [18]. HDL cholesterol also tends to be very low in these patients, which could impair reverse cholesterol transport and other potential benefits of HDL [18]. It has also been proposed that, irrespective of its catalytic activity, lipoprotein lipase (LPL) itself may act to retain LDL and VLDL in the arterial intima, promote their adherence to the extracellular matrix and enhance macrophage uptake of lipoproteins and the development of foam cells [18]. It has

also been proposed that these functions of LPL may be preserved even in patients with deficient LPL hydrolysis, as long as the size of the molecule remains relatively intact, as is the case for many patients with familial chylomicronemia [18]. However, the controversy regarding the risk of atherosclerosis in familial chylomicronemia has not yet been definitively resolved.

*Laboratory Features* Plasma drawn from individuals with familial chylomicronemia appears turbid (lipemic) and milky (Fig. 11.1) [10]. If left to settle and refrigerated overnight, it will develop a creamy supernatant above a clear infranatant [1–3]. Fasting serum TG is generally >10 mmol/L (>900 mg/dL), and sometimes can exceed 100 mmol/L (9000 mg/dL) [19]. Concomitant lipid abnormalities include a modest elevation in serum total cholesterol, and decreases in LDL and HDL cholesterol [1–3].

*Molecular Basis* Mutations in five different genes cause familial chylomicronemia (Table 11.3), of which, by far, the most common is *LPL* encoding LPL. In earlier times, a diagnosis of LPL deficiency was established biochemically by the absence of LPL activity in plasma collected after intravenous heparin injection [19, 20]. Presently, the diagnosis is made more commonly by DNA sequence analysis showing the presence of mutations on both *LPL* alleles leading to complete LPL deficiency [18]. Reported mutations in LPL associated with severe HTG are shown in Fig. 11.2. LPL normally hydrolyses TG transported in TG-rich lipoproteins to liberate free fatty acids for TG resynthesis and storage in adipose tissue or beta-oxidation in skeletal muscle and heart [19, 20]. In total, >118 homozygous or compound heterozygous *LPL* mutations have been shown to cause LPL deficiency in patients [20] (Fig. 11.2).

Interestingly, the four other genes associated with monogenic HTG all play a role in activity, assembly or transport of LPL (see Table 11.3). Apo C-II is an essential LPL coactivator absolutely required for TG-rich lipoprotein hydrolysis [4–6, 21], thus homozygous mutations in *APOC2* cause apo C-II deficiency and monogenic HTG
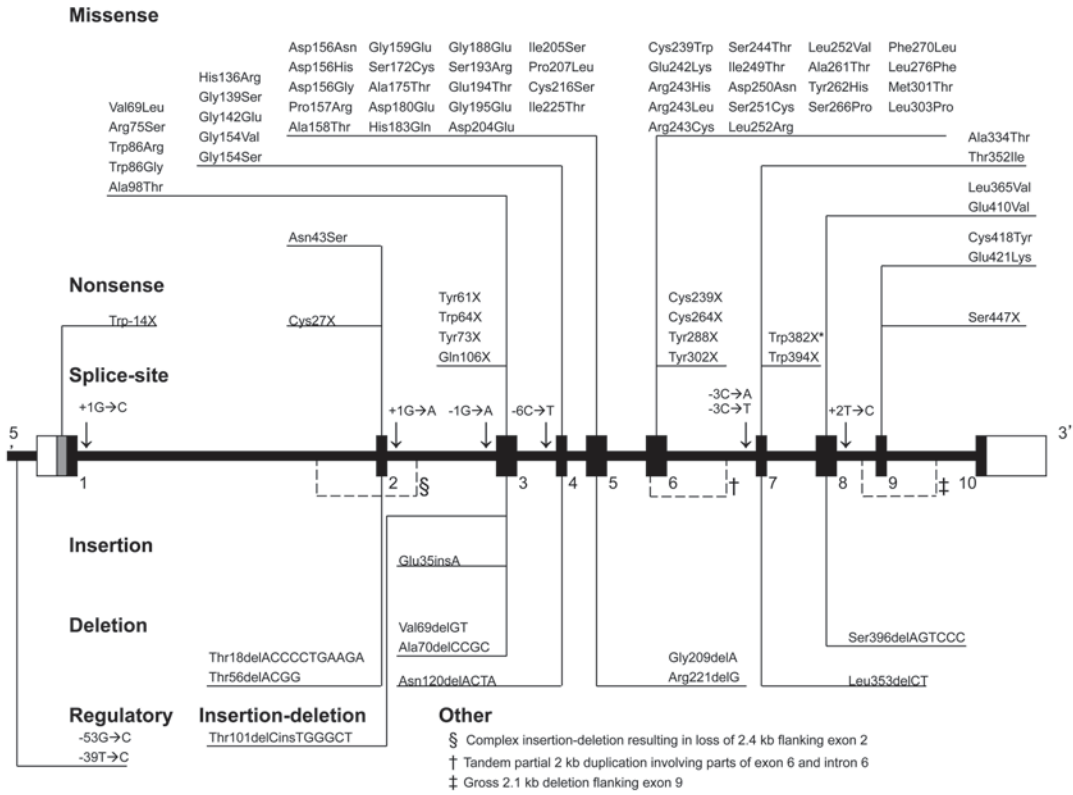
**Fig. 11.2** Lipoprotein lipase (LPL) deficiency-causing mutations in the LPL gene. *Black boxes* denote exons, *gray box* denotes 27 codon signal sequence, and *white boxes* denote untranslated regions. (Figure from [20])

**Table 11.3** Genes associated with familial chylomicronemia

| Gene | Disease frequency | TG levels (mmol/L) | Onset | Genetic inheritance | Molecular basis |
|---|---|---|---|---|---|
| Lipoprotein lipase (*LPL*) | 1 in 1 million (95% of cases) | >40–120 | Infancy or childhood | Autosomal recessive | Severely reduced or absent LPL enzyme activity |
| Apolipoprotein C-II (*APOC2*) | <20 families described | >40–120 | Adolescence to adulthood | Autosomal recessive | Absent or non-functional apo C-II, a key cofactor for LPL |
| Glycosyl-phos-phatidyl-ino-sitol-anchored HDL-binding protein (*GPIHBP1*) | <15 families described | <155 | Infancy to Late adulthood | Autosomal recessive | Absent or deficiency in GPIHBP1, a CM anchor-ing protein and facilitator of LPL activity |
| Apo A-V (*APOA5*) | <5 families described | <130 | Late adulthood | Autosomal recessive | Absent or defective Apo A-V, and facilitator of LPL activity |
| Lipase matura-tion factor-1 (*LMF1*) | <5 families described | <130 | Late adulthood | Autosomal recessive | Defective or absent LMF1, a chaperone protein for LPL |

Abbreviations: as in Tables 11.1 and 11.2

**Table 11.4**   Treatment strategies for hypertriglyceridemic states

| Condition | Lifestyle modifications | Risk factor control | Medications | Experimental/ Other |
|---|---|---|---|---|
| Familial chylo-micronemia | Low-fat diet ($<$20–50 g/d) | Avoid alcohol, obesity, exogenous estrogens, and steroids | Fibrates may be helpful in patients with partial LPL deficiency | Plasmapheresis for pancreatitis treatment and prophylaxis |
| | | Improved control of diabetes, hypothyroidism | | Gene therapy with virus-recombinant LPL |
| Dysbetalipo-proteinemia | Weight loss | Improved control of diabetes, hypothyroidism | Fibrates, Statins, Niacin and omega 3 fatty acids may have some utility | |
| | Reduced fat diet | | | |
| Simple primary hypertriglyc-eridemia | Appropriate caloric intake | Improved control of diabetes | Fibrates | |
| | Decreased fat/ saturated fat intake | Improved control of cardiovascular risk factors (hypertension, obesity, smoking) | Niacin | |
| | Reduced carbohydrate intake | | Omega-3 fish oils | |
| | Increased physical activity | | | |
| Mixed hyper-lipidemia | Dietary fat restriction | Reduce alcohol intake | Fibrates | |
| | Weight control | Improved control of diabetes, hypothyroidism | Niacin | |
| | | | Omega- 3 fish oils | |
| | | | (Statins) | |

*LPL* lipoprotein lipase

[4–6, 21]. *APOC2* mutations (defined at the amino acid level) were the first human mutations reported in patients with any dyslipidemia [21]. Apo A-V is also required for efficient lipolysis of TG-rich particles by LPL [22], although its precise mechanism of action is unknown. Homozygous mutations in *APOA5* causing apo A-V deficiency cause severe HTG [22]. Homozygous mutations in genes that are required for efficient assembly and transport of LPL, including *GPI-HBP1* [23] and *LMF1* [24], were also recently shown to cause monogenic HTG.

*Treatment Strategies* The treatment of patients with severe HTG due to familial chylomicro-nemia follows the general principles for treating HTG outlined below, including dietary and lifestyle interventions, control of secondary factors, and pharmacological therapies (Tables 11.4 and 11.5). Unfortunately, current pharmacologic therapies that are effective for milder HTG states are less effective for familial chylomicronemia [1, 15]. In addition, because of the severe elevation of HTG and imminent risk of pancreatitis, further special treatment is indicated for patients with familial chylomicronemia, starting with significant fat restriction.

The current recommended targets for dietary management of familial hyperchylomicrone-mia are variable and range from the most liberal advice of $<$50 g of dietary fat intake per day, or $<$25 % of daily caloric intake, to $<$20 g per day, or $<$10 % of total daily caloric intake [1–3]. Unfortunately, these extreme dietary restrictions are usually difficult for patients to follow, and consequently success has been variable. Avoidance of triggers or causes of secondary HTG is also of utmost importance in these pa-

**Table 11.5** Medications for hypertriglyceridemia (HTG)

| Medication | Effect on lipid profile | Mechanism of action | Side effects |
| --- | --- | --- | --- |
| Fibrates | ↓TG 30–50% | Increase LPL activity and synthesis | GI intolerance |
| | ↑HDL cholesterol by up to 20% | Decrease hepatic VLDL production through PPAR-α | Increase risk of cholesterol gallstones |
| | Variable LDL effects | | Interaction with statins |
| Niacin | ↓TG 10–30% | Decrease fatty acid flow to liver and VLDL production | Flushing/lightheadedness/ Pruritis |
| | ↑HDL 10–40% | Increase LPL activity | Worsen glucose intolerance |
| | ↓LDL 5–20% | | Can cause hyperuricemia and worsen gout |
| Omega 3 fish oils | ↓TG 20–50% ↑HDL 5% | Reduced hepatic TG synthesis | Fishy taste, burping |

*TG* triglyceride, *HDL* high-density lipoprotein, *VLDL* very low-density lipoprotein, *GI* gastrointestinal, *PPAR-α* peroxisome proliferator-activated receptor-alpha, *LPL* lipoprotein lipase

tients. These include alcohol, obesity, exogenous estrogens, and certain other medications such as corticosteroids and retinoids [1]. Pregnancy, hypothyroidism, diabetes, and chronic renal failure are also conditions which can worsen HTG and put patients at greater risk of developing pancreatitis [1].

Case reports suggest that plasmapheresis and direct removal of serum TG from patients experiencing acute pancreatitis may be of some clinical utility [25]. While the procedure seems to be very well tolerated with no major complications reported [25], it is expensive and requires specialized equipment and knowledgeable staff [25]. Further, in our experience, patients with severe chylomicronemia who are treated in hospital with cessation of all oral intake of calories and fluid replacement show just as rapid improvement in their plasma TG levels (reduction by half every 48–72 h) as patients who are treated with plasma exchange or plasmapheresis.

Finally, recent efforts have focused on the potential of gene therapy as a long-term cure for familial chylomicronemia patients. Expression of a virus-recombinant human gain-of-function LPL mutant S447X has shown promise in restoring LPL function in murine models [26]. Early clinical trials in human subjects using intramuscular injections of recombinant LPL were successful at inducing local LPL expression and resulted in a transient reduction in plasma TG levels and reduced incidence of pancreatitis [27].

This treatment (trade name Glybera) was recently approved by the European Medicines Agency for the treatment of HLP type 1 due to LPL deficiency [28].

## Polygenic HTG: Common Genetic Basis for Complex HTG Phenotypes

Molecular genetic studies in our lipid clinic patients suggest that HLP types formerly known as 2B, 3, 4, and 5 all have a similar multigenic or polygenic background. Polygenic HTG has a complex genetic etiology consisting of common small effect variants and rare heterozygous large-effect variants in genes associated with plasma TG concentration [4–7]. We suggest that the disorder formerly known as HLP type 4 is the foundational HTG phenotype, and it results from the accumulation of both common and rare genetic variants that contribute to susceptibility to raised TG levels. Patients with the clinically more severe HLP type 5 have the same genetic predisposition as HLP type 4, with an additional burden of alleles or additional secondary or metabolic stress. Most patients with HLP type 3 are essentially HLP type 4 patients with the overlaid contribution of one additional genetic variant, namely the *APOE* E2/E2 genotype [8]. Finally, the overlay of common LDL-associated alleles on polygenic HTG susceptibility pushes the clinical phenotype in the direction of HLP type 2B [7, 8].

**Table 11.6** Top ten common DNA polymorphisms associated with hypertriglyceridemia (HTG)

| CHR | Gene | SNP | Risk allele | OR (95 % CI) | P-value |
|---|---|---|---|---|---|
| 11 | *APOA5* | rs964184 | G | 3.43 (2.72–4.31) | $1.12 \times 10^{-25}$ |
| 2 | *GCKR* | rs1260326 | T | 1.64 (1.36–1.97) | $1.97 \times 10^{-7}$ |
| 8 | *LPL* | rs12678919 | A | 2.21 (1.52–3.22) | $3.5 \times 10^{-5}$ |
| 8 | *TRIB1* | rs2954029 | A | 1.50 (1.24–1.81) | $3.8 \times 10^{-5}$ |
| 1 | *ANGPTL3* | rs2131925 | T | 1.51 (1.23–1.85) | $1.0 \times 10^{-4}$ |
| 7 | *MLXIPL* | rs7811265 | A | 1.63 (1.25–2.13) | $3.3 \times 10^{-4}$ |
| 4 | *KLHL8* | rs442177 | T | 1.36 (1.13–1.64) | $1.5 \times 10^{-3}$ |
| 10 | *CYP26A1* | rs2068888 | G | 1.29 (1.08–1.55) | $5.9 \times 10^{-3}$ |
| 19 | *CILP2* | rs10401969 | T | 1.72 (1.16–2.54) | $6.8 \times 10^{-3}$ |
| 2 | *APOB* | rs1042034 | T | 1.28 (1.02–1.61) | 0.032 |

*CHR* chromosome, *SNP* single nucleotide polymorphism, *OR* odds ratio for hypertriglyceridemia per risk allele, *CI* confidence interval, *APOA5* gene encoding apolipoprotein A-V, *LPL* gene encoding lipoprotein lipase, *TRIB1* gene encoding Tribbles homolog 1, *ANGPTL3* gene encoding angiopoietin-like protein 3, *MLXIPL* gene encoding MLX interacting protein-like 1, *KLHL8* gene encoding Kelch like protein 8, *CYP26A1* gene encoding cytochrome P450 26A1, *CILP2* gene encoding cartilage intermediate layer protein 2, *APOB* gene encoding apolipoprotein B (data from reference 31)

The gold-standard panel of replicable small-effect common variants that raise plasma TG levels are the 32 TG-associated loci from the Global Lipids Genetics Consortium [28]. The largest effects among these are at the *APOA5, LPL, GCKR,* and gene encoding apolipoprotein B (*APOB*) loci, for which the deleterious alleles raise TG levels by 0.05–0.20 mmol/L in the general population [28]. These same alleles increase HTG risk by two- to fourfold in lipid clinic patients [29]. A list of the top ten common single nucleotide polymorphism (SNP) alleles that are associated with HTG risk are shown in Table 11.6. A patient's total genomic burden of the risk alleles can be tallied to create a "genetic risk score" (GRS) for HTG susceptibility [28, 29]. GRSs can be raw (simple allele counts) or weighted, in which there is a further adjustment based on the degree of TG elevation caused by the specific risk allele: Alleles with larger effects on TG levels contribute more to the weighted GRS.

Groups of HTG patients have significantly higher mean GRS than normolipidemic patients [28, 29]. However, there is a very wide range of GRS around these means and considerable overlap of GRS between individual HTG and normolipidemic subjects. The GRS discriminates well between HTG and normolipidemic subjects at the extremes of the distribution but there is substantial overlap through the middle of the distribution [4–7]. Nonetheless, the potential diagnostic util-ity of the GRS is less important than the principle that the HTG population has a higher burden of small-effect common genetic polymorphisms, which form the basis of genetic susceptibility to most HTG states [4–7].

In addition to common small effect variants, patients with HTG also have a higher burden of rare large effect variants [30, 31]. Again, these are significantly more prevalent in the pool of HTG patients, but they are not diagnostic for the development of HTG in any particular individual. Further, the variants generally do not cosegregate with TG levels in family pedigrees. Individuals who carry a higher burden of variants are relatively rare even in the population of HTG patients—frequencies of such individuals approximate those of carriers of mutations for rare Mendelian diseases [30, 31].

## Simple Primary Hypertriglyceridemia (HLP Type 4)

We suggest the term "simple primary HTG" for the disorder formerly known as "familial HTG" or HLP type 4. This relatively common phenotype is characterized by high TG levels due to an isolated elevation of VLDL particles, which results from both overproduction and decreased elimination of these particles [4–7]. Susceptibility to simple HTG results from a heterogeneous

group of mechanisms that cause elevations in VLDL [4–7, 31].

*Epidemiology* TG levels elevated to between 3.4 and 9.9 mmol/L due to an isolated elevation of VLDL particles is seen in up to 5% of adults [1, 3].

*Clinical Features* Simple primary HTG is associated with an increased risk of CVD, obesity, insulin resistance or frank diabetes, and is associated with hypertension and hyperuricemia [1]. With an additional metabolic stress, simple HTG patients can deteriorate into mixed hyperlipidemia (HLP type 5), with fasting chylomicronemia. Generally, the TG levels resulting from VLDL excess in simple primary HTG are not high enough to cause pancreatitis [15].

*Laboratory Features* Patients with simple HTG have moderately elevated plasma TG levels, on the order of 3.3–9.9 mmol/L [1]; these are frequently associated with depressed HDL cholesterol [1]. At the higher end of the TG range for this condition, serum may also appear turbid on examination due to the presence of large VLDL particles [1].

*Molecular Basis* The molecular basis for simple primary HTG follows the polygenic architecture for most "familial" HTG states, as described above, sometimes with the presence of one or more secondary factors that can force expression of the phenotype in a genetically susceptible person [4–7, 31]. The fundamental genetic susceptibility component, as described above, is an increased burden of common, small effect variants that individually raise TG levels by a fraction of a mmol/L in studies conducted in the general population. Such common variants tend to cluster in families, but the combinations of variants, because they are on different chromosomes, segregate independently and thus the susceptibility to HTG does not pass from parent to child in a clear Mendelian fashion [30, 31]. In addition, occasional heterozygous rare variants are seen at increased frequency in the pool of HTG subjects, but these also do not clearly cosegregate with HTG in family pedigrees.

*Treatment Strategies* Treatment of simple HTG follows the general strategy outlined below.

## Dysbetalipoproteinemia (HLP Type 3)

Dysbetalipoproteinemia, also known as HLP type 3 or remnant removal disease, is characterized by increased serum TG and cholesterol rich lipoprotein remnants—essentially IDL and chylomicron remnants, sometimes collectively called beta-VLDL particles [1, 32]. These particles are usually rich in apo E. Dysbetalipoproteinemia is mainly caused by homozygosity for binding-defective apo E2 isoform on a background of genetic susceptibility to HTG that resembles HLP type 4 [32].

*Epidemiology* Dysbetalipoproteinemia affects ~1 in 10,000 people [1, 32]. The condition generally does not present until adulthood for men and in the postmenopausal years in women, and is more common in men overall [1, 32].

*Clinical Features* Nowadays, patients with dysbetalipoproteinemia tend to be identified early biochemically and then treated, so few of them have the classical physical stigmata (Fig. 11.3). Patients in the fourth decade of life or older who have not been treated can present with tuberous or tuberoeruptive xanthomas on the extensor surfaces of the extremities, such as on the elbow and knees and occasionally the buttocks [1, 32]. Planar or palmar crease xanthomas are also noted [32]; these appear as orange lipid deposits seen in the crease areas of the palm and are pathognomonic of familial dysbetalipoproteinemia, however they are not present in all individuals with the condition [1].

Patients with dysbetalipoproteinemia have increased risk of both coronary artery disease (CAD) and peripheral vascular disease (PVD) [1, 32]. Remnant and IDL particles are atherogenic, so that even in the context of reduced LDL cholesterol, dysbetalipoproteinemia patients are elevated risk of CAD and PVD [32]. Dysbetalipoproteinemia often requires secondary factors for overt disease expression. These include ad-
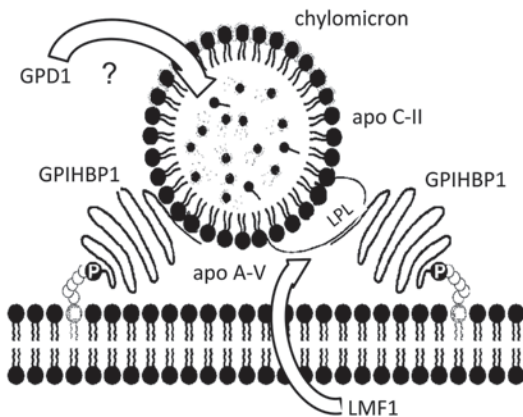
**Fig. 11.3** Proteins with naturally occurring mutations that can affect the function of LPL and lipolysis, leading to familial chylomicronemia. The circulating triglyceride (TG)-rich chylomicron is shown in the *center* of the figure. Lipoprotein lipase (*LPL*) is the key enzyme that is involved in hydrolysis of TG within chylomicrons, and is shown tethered to the endothelial cell surface by glycosylphosphatidylinositol anchored high-density lipoprotein binding protein 1 (*GPIHBP1*). Among the apolipoprotein constituents of chylomicrons are apolipoproteins C-II and A-V (apo C-II and apo A-V, respectively), which enable the normal functioning of LPL. LPL undergoes maturation within cells with chaperone protein lipase maturation factor 1 (*LMF1*) which is responsible for bringing LPL to the endothelial cell surface. Mutations on both alleles of *LPL, GPIHBP1, APOC2, APOA5,* or *LMF1* genes that lead to loss-of-function of the respective gene products can lead to impaired lipolysis of chylomicrons and fasting chylomicronemia. Cytosolic glycerol-3-phosphate dehydrogenase (GPD1) is an NAD+-dependent enzyme that reduces dihydroxyacetone phosphate to glycerol-3-phosphate. The mechanism whereby homozygous mutations in the *GPD1* gene lead to chylomicronemia is currently unknown. (Figure adapted from Young SG, Davies BS, Fong LG, Gin P, Weinstein MM, Bensadoun A, Beigneux AP. GPIHBP1: an endothelial cell molecule important for the lipolytic processing of chylomicrons. Curr Opin Lipidol. 2007;18:389–96)

ditional genetic susceptibility variants, or other hormonal or environmental factors, such as the presence of disorders such as obesity, type 2 diabetes or hypothyroidism [32].

*Laboratory Features* Patients with dysbetalipoproteinemia typically present with elevated total cholesterol levels, generally between 6–11 mmol/L (240–450 mg/dL) with elevated TG also in the range of 3–10 mmol/L (250–900 mg/dL) [1, 32]. The levels of total cholesterol and TG are generally roughly equally elevated [1]. When directly measured, LDL cholesterol is typically low due to disrupted processing of VLDL to LDL [1, 8, 32]. The major component of circulating TG is in the form of IDL [32], but other remnant subfractions are increased. VLDL particles also tend to be cholesterol-enriched, which can be determined by ultracentrifugation of isolated VLDL particles [1].

*Molecular Basis* Similar to other HTG states, dysbetalipoproteinemia is a polygenic trait. These patients have a similar background of increased genetic susceptibility seen in simple HTG (HLP type 4). But in addition, dysbetalipoproteinemia patients have additional genetic variants or mutations that affect the normal function of apo E [1, 32]. Usually, dysbetalipoproteinemia patients are homozygous for the apo E2 allele variant or protein isoform, which binds abnormally to cell surface receptors, such as the LDL receptor [8, 32]. The common apo E allele is the apo E3 isoform, which differs from E2 by the presence of an arginine at residue 158 in the receptor-binding domain, while E2 contains a cysteine at this position [8, 32]. Less commonly—<5% of dysbetalipoproteinemia patients—will have rare dominant mutations in *APOE* [1, 8]. Such rare *APOE* mutations may not require secondary causes to express the dysbetalipoproteinemia phenotype [8]. The *APOE* mutations in dysbetalipoproteinemia result in elevated serum β-VLDL particles patients through impaired hepatic uptake of apo E-containing lipoproteins, such as CM remnants and IDL particles, and also cause a reduction in the conversion of VLDL and IDL to LDL particles [1].

*APOE* mutations are necessary for the expression of dysbetalipoproteinemia, but are not sufficient on their own to elicit the phenotype [8, 32]. In fact, <10% of homozygotes for the binding-defective E2 isoform develop dyslipidemia [32]. Therefore, additional factors, which we now believe to be the burden of HTG susceptibility arising from accumulation of common and rare HTG-associated alleles, or secondary factors, such as diabetes, hormonal disturbances

or obesity, are usually required for phenotypic expression of the phenotype [1, 32]. Two of the most replicated susceptibility variants are within the *APOA5* gene, namely S19W and −1131T > C, which are also the most strongly associated SNPs seen with other HTG-containing phenotypes [7, 33].

*Diagnosis* Dysbetalipoproteinemia is suggested in patients who have equimolar elevations of total cholesterol and TG [32]. When fractionation methods, such as ultracentrifugation and electrophoresis are available, the presence of a broad beta band or of IDL, are both suggestive of this phenotype. Another diagnostic test is an elevated ratio of VLDL-cholesterol to total TG; again this requires specialized biochemical testing methods that are becoming less commonly available. An elevated VLDL cholesterol to total TG ratio (>0.3) along with apo E2/E2 homozygosity or another rare *APOE* mutation are pathognomonic for dysbetalipoproteinemia [1, 32].

*Treatment Strategies* Treatment of dysbetalipoproteinemia follows the general strategy for HTG outlined below. In addition, some of these patients are quite sensitive to weight loss, reduced fat diets and alleviation of secondary conditions, such as type 2 diabetes and hypothyroidism [1]. In our experience, these patients are also quite responsive to a wide range of pharmacological treatments, including fibrates, niacin, fish oil, and statins.

## Mixed Hyperlipidemia (HLP Type 5)

Mixed hyperlipidemia, or HLP type 5, is, like HLP type 1, also characterized by the pathologic presence of chylomicrons in the serum after 12–14 h of fasting [1]. But in addition, HLP type 5 has elevated levels of VLDL particles, like HLP type 4. The phenotype is essentially a more extreme form of HLP type 4, in which chylomicrons accumulate during fasting.

*Epidemiology* Mixed hyperlipidemia has a population prevalence of ~1 in 600 [1–3]. A key

distinguishing feature between mixed hyperlipidemia and familial chylomicronemia is the age of onset of presentation. Patients with familial chylomicronemia typically present in childhood or adolescence, whereas mixed hyperlipidemia patients typically present in adulthood [1, 4–7]. Inheritance pattern is variable, with the phenotype thought to be triggered in patients with an underlying genetic susceptibility coupled with the influence of environmental and hormonal exposures [1, 4–7].

*Clinical Features* These are similar to those seen in familial chylomicronemia, with eruptive xanthomata, lipemia retinalis, hepatosplenomegaly, and a greatly increased risk of developing pancreatitis [1]. Other features include neurological symptoms, such as the inability to concentrate [3], although this feature is variable and the underlying mechanism is not understood.

*Laboratory Features* The laboratory findings in primary mixed hyperlipidemia are similar to those seen with familial chylomicronemia, with an elevated fasting serum level of chylomicrons, typically >10 mmol/L (>900 mg/dL), together with elevated levels of VLDL particles [1, 8]. Plasma appears turbid, and develops a creamy supernatant when allowed to stand overnight [1]. Patients with primary mixed hyperlipidemia also have associated elevations in total cholesterol, and often other lipoproteins, particularly VLDL, which are not present in familial chylomicronemia [1, 8].

*Molecular Basis* HLP type 5 shares much of the same genetic susceptibility from common and rare TG-associated alleles that have accumulated in the genomes of affected individuals [1, 8]. We have observed that patients with HLP type 5 carry a greater burden of the common susceptibility alleles than patients with HLP type 4 [31].

*Treatment Strategies* Treatment of mixed dyslipidemia follows the general strategy for HTG outlined below, including weight loss, restriction of total calories, simple carbohydrates, trans and saturated fats, and alcohol. In addition, treat-

ments for primary mixed hyperlipidemia are focused on reversing or controlling any potential triggers for the condition, such as eliminating any medications known to worsen the condition, and maintaining optimal control of hypothyroidism and diabetes [3, 34]. Pharmacological management is also an option for these patients. Medications that can be useful in treatment of these patients include fibrates, nicotinic acid and fish oils, as discussed below [3, 34]. The chylomicronemia in this condition places patients at risk of pancreatitis; if this develops, the principles of management are similar to those discussed above for familial chylomicronemia.

## Combined Hyperlipidemia (HLP Type 2B)

Although this condition is the topic of another chapter, it is worth reemphasizing here the concept that the genetic architecture of this phenotype is determined by polygenic susceptibility to both HTG and high LDL cholesterol levels, through accumulation of SNP risk alleles for both biochemical disturbances based on higher GRS for each trait. There are a few monogenic forms of combined hyperlipidemia due to single gene effects that appear to segregate in families and have been replicated [7, 31]. But by and large, as with the other complex HTG states, there is no clear monogenic determinant of this common and complex phenotype.

## General Treatment Approaches for HTG (Tables 11.4 and 11.5)

### Nonpharmacological Treatment

There are certain common elements for management of all HTG states [1]. The cornerstone of treatment for HTG patients is diet, weight loss, reduction of alcohol intake and control of secondary metabolic factors, such as hyperglycemia. Treatment is focused on dietary control including monitoring of caloric intake, reduced fat, especially saturated fat, consumption, as well

as reduction in carbohydrate intake, especially in the form of high glycemic or high fructose foods [34]. Alcohol raises TG levels in susceptible people, and reduction or elimination of alcohol intake is also an important component of treatment in patients with HTG. Increased levels of physical activity have also been shown to be helpful to lower TG levels [35]. Control of risk factors and other underlying conditions is also helpful in these patients. Improved glycemic control in diabetes, control of other cardiovascular risk factors, such as obesity and hypertension, and discontinuation of smoking are all helpful in HTG patients [1].

## Fibrates

Fibrates, such as gemfibrozil, bezafibrate, and fenofibrate, reduce TG levels by 30–50%, and can also raise HDL cholesterol by up to 20% [1, 3, 17, 36]. The effect of fibrates on serum LDL is variable, in some HTG patients fibrates can increase LDL cholesterol [1, 3, 17, 36]. Fibrates are considered important as prophylactic treatment against pancreatitis [1, 3, 17, 36]. There have been no studies, however, that have shown a definitive reduction in cardiovascular outcomes or total mortality in this population [1, 15].

Fibrates act by increasing fatty acid oxidation through LPL, increasing LPL synthesis, and reducing apo C-III expression, which acts to decrease VLDL production and increase LPL-mediated breakdown of TG-rich particles [36]. Fibrates have been shown to act in the liver on the peroxisome proliferator-activated receptor-alpha (PPAR), which acts to lower hepatic production of VLDL [36].

Side effects of fibrates include gastrointestinal intolerance, and a slight increased incidence of cholesterol gallstones [1, 36]. There are also rare reports of fibrate use leading to hepatitis and myositis [36], especially for gemfibrozil when used in combination with statins that are metabolized through the CYP 3A4 pathway [36]. In contrast, fenofibrate can be safely combined with statins [36].

## Nicotinic Acid (Niacin)

Although nicotinic acid, or niacin, has been shown to reduce TG levels by only 10–30%, it has been shown in some studies to reduce the risk of cardiovascular events and the development of atherosclerosis [31]. However, more recent studies, including the randomized controlled AIM-HIGH trial, reveal no further benefits beyond those gained from a statin alone [37]. Nicotinic acid also increases HDL cholesterol by ~10–40%, and lowers LDL cholesterol by ~5–20% [37].

The lipid-lowering mechanism of action of niacin is unknown: the dogma that it reduces the flux of fatty acids to the liver and thus reduces VLDL secretion by the liver has been called into question recently [38]. Niacin also acts in adipose tissue by increasing the sensitivity of LPL for TG and in the liver by inhibiting diacylglycerol acyltransferase-2 (DGAT-2) leading to decreased VLDL secretion [39]. It also stimulates the production of apo A1 in the liver, which results in a modest HDL cholesterol increase [39].

Unfortunately, niacin has use-limiting side effects, such as flushing, lightheadedness, and pruritis, which can occur shortly after administration of the drug and can last from 15–30 min [39]. Rarely, niacin can also cause hepatotoxicity or elevation of liver enzymes [1]. It can also worsen glucose intolerance, and should be used with caution in prediabetics, or overt diabetes with poor glycemic control [39]. It can also raise levels of uric acid in the blood, which may precipitate or worsen gout [39].

## Statins

Statins, or 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG CoA) reductase inhibitors, are most often used to treat elevated levels of total of LDL cholesterol, and are not typically used as first line agents with TG levels >5 mmol/L [1]. However, there is copious evidence in support of statins reducing risk of CVD endpoints [40]. Statins are generally well tolerated but can occasionally cause myopathy and rarely rhabdomy-olysis [40]. Statins can also interact with certain fibrates, especially gemfibrozil, so this particular combination should be avoided [36]. Statins may be considered for use in patients with HTG who may be at risk for CAD, in order to improve their CVD risk.

## Omega-3 Fatty Acids

Omega 3 fatty acids, especially in the form of eicosapentaenoic acid (EPA) have been shown to reduce serum TG levels by 20–50% [41]. They also modestly raise HDL cholesterol by ~5% [41]. There is some evidence that reduced TG levels are associated with increases in low-density lipoprotein cholesterol (LDL-C), and no trials have yet demonstrated the effectiveness of omega 3 fatty acids in improving CVD outcomes [41]. The mechanism of action of omega 3 fatty acids is unclear [41]. Side effects associated with omega 3 fatty acids are minimal, and include fishy taste and burping (eructation) [41].

## Conclusion

HTG is a commonly encountered clinical phenotype that is relevant because: (1) modestly elevated TG are associated independently with increased risk of CVD; (2) severely elevated TG are associated with increased risk of pancreatitis; and (3) HTG is often associated with other metabolic disturbances that are associated with increased cardiometabolic risk. Both genetic and nongenetic factors contribute to the development of HTG. However, the only truly monogenic form of HTG is HLP type 1 or familial chylomicronemia, which is associated with mutations in at least five separate genes. The other HTG states are polygenic or multigenic and typically require additional environmental, genetic, lifestyle or hormonal influences to manifest themselves clinically. The mainstay of treatment currently for all HTG states is control of risk factors, diet, and lifestyle choices to ensure maximal health for HTG patients, medication can also be useful in select populations. Ongoing research, especially

into gene therapy for familial chylomicronemia, may lead to long-term improvements in quality and length of life for patients with this rare monogenic phenotype.

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