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Case Series

Phenotypic Heterogeneity of Familial Hypertriglyceridemia: A Case Series of a Mother and Three Siblings with Diverse Clinical Outcomes

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ABSTRACT

Background: Familial hypertriglyceridemia (FHTG) is a common autosomal dominant lipid disorder characterized by elevated plasma triglycerides (TG). According to the AHA/ACC 2018 and ESC/EAS 2019 guidelines, TG levels are classified as borderline high (150–199 mg/dL), high (200–499 mg/dL), severe (500–999 mg/dL), or very severe (≥1000 mg/dL). Its clinical expression is highly variable even within the same family, influenced by secondary factors including diet, obesity, diabetes, alcohol intake, and medications.

Case Description: We present a case series of four family members — a 63-year-old mother (proband) and her three children aged 28, 33, and 41 years — all exhibiting hypertriglyceridemia with markedly different TG levels (118–1061 mg/dL), comorbidity burden, and clinical outcomes. Target TG levels for therapy are <150 mg/dL (normal), or <500 mg/dL as an urgent target to prevent acute pancreatitis in patients with severe hypertriglyceridemia. All family members are currently managed with fenofibrate, with variable degrees of TG control: the mother has achieved the therapeutic target (<150 mg/dL), the first daughter and brother demonstrate persistent elevation above target despite pharmacotherapy, and the youngest daughter exhibits persistent severe hypertriglyceridemia despite pharmacotherapy (TG 1061 mg/dL, far exceeding the ≥1000 mg/dL very-severe threshold).

Discussion: This family illustrates the remarkable phenotypic heterogeneity of FHTG. The proband has achieved good TG control despite significant cardiovascular comorbidities, while the youngest sibling presented with persistent severe hypertriglyceridemia complicated by pregnancy, necessitating substitution of fenofibrate with omega-3 fatty acids and lifestyle modification. The 33-year-old male sibling developed premature cardiovascular disease (microvascular dysfunction) and type 2 diabetes mellitus (T2DM) at a young age, underscoring the metabolic risks associated with persistent severe hypertriglyceridemia despite pharmacotherapy. Analysis of extended family lipid profiles — including LDL-cholesterol, HbA1c, HDL-cholesterol, and uric acid — further reveals the spectrum of atherogenic dyslipidemia within this kindred.

Conclusion: Cascade screening of first-degree relatives of patients with FHTG is critical, with particular urgency in Asian populations given distinct dietary patterns and genetic predispositions to hypertriglyceridemia. Management must be individualized, particularly in special populations such as pregnant women. This case series highlights the necessity of long-term, family-centered approaches to lipid management.

Keywords: Familial Hypertriglyceridemia, Phenotypic Heterogeneity, Fenofibrate, Omega-3 Fatty Acids, Cardiovascular Risk, Pregnancy, Microvascular Disease, APOA5, LPL Variants, Asian Populations

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INTRODUCTION

Hypertriglyceridemia is defined as a fasting serum triglyceride concentration above 150 mg/dL (Brahm & Hegele, 2013). In accordance with the AHA/ACC 2018

Cholesterol Guideline (Grundy et al., 2019) and ESC/EAS 2019 Dyslipidaemia Guidelines (Mach et al., 2020), the current classification is as follows: borderline high (150–199 mg/dL), high (200–499 mg/dL), severe (500–999 mg/dL), and very severe (≥1000 mg/dL). The prior Fredrickson classification system, while historically significant, has been superseded by these contemporary frameworks that better integrate cardiovascular and pancreatitis risk. FHTG is a monogenic or oligogenic disorder transmitted in an autosomal dominant pattern, with a prevalence of approximately 1 in 500 individuals in the general population (Cruz-Bautista et al., 2021; Hegele et al., 2014).

The clinical expression of FHTG is highly variable. Some affected individuals may present with only mildly elevated TG, while others may develop pancreatitis-level hypertriglyceridemia. This variability is partly attributable to the interplay between underlying genetic susceptibility and modifying secondary factors such as T2DM, obesity, hypothyroidism, renal disease, alcohol consumption, and medications. At the molecular level, the majority of causative variants impair lipoprotein lipase (LPL)-mediated hydrolysis of TG-rich lipoproteins — a process regulated by activating cofactors (apolipoprotein C-II [APOC2], apolipoprotein A-V [APOA5]) and anchoring proteins (GPIHBP1, LMF1) — resulting in accumulation of chylomicrons and very low-density lipoprotein (VLDL) particles in the circulation.

Special attention is warranted in Asian populations, including Southeast Asian patients, in whom dietary carbohydrate and refined sugar intake is typically high, genetic polymorphisms in APOA5 (particularly the −1131T>C variant) are more prevalent (Jiang et al., 2010), and the metabolic threshold for hypertriglyceridemia expression may be lower than in European cohorts. These factors underscore the urgency of early detection and proactive cascade family screening in this demographic.

The cardiovascular implications of FHTG are well established. Elevated TG levels, particularly when associated with low HDL-cholesterol and increased atherogenic remnant particles, confer increased cardiovascular risk (Goldberg et al., 2011; Miller et al., 2011). TG levels ≥500 mg/dL substantially increase the risk of acute pancreatitis (Rawla et al., 2018). We present a family case series illustrating the phenotypic spectrum of FHTG across a mother and three adult children, highlighting diverse clinical manifestations, comorbid conditions, and management challenges — including treatment during pregnancy.

CASE PRESENTATIONS

Summary Overview

Table 1 provides a comparative overview of all four family members, including their TG levels relative to the therapeutic target of <150 mg/dL and the urgency threshold of <500 mg/dL for pancreatitis prevention.

Table 1. Comparative clinical summary of the family.

Patient	Age	TG 2026 (mg/dL)	Target TG (mg/dL)	TG Control	Key Comorbidities
Mother (Proband)	63 y	118	<150	At target	CAD/3VD, DM T2, HHD, Dyslipidemia
Daughter 1	41 y	232	<150	Above target	Hypertriglyceridemia only
Son (Brother)	33 y	462	<500 (urgent)	Above therapeutic target; below urgency threshold*	CAD Microvascular, DM T2, HHD
Daughter 2	28 y	1061	<500 (urgent)	Persistent severe HTG despite pharmacotherapy	HTN; prior pregnancy

TG = Triglycerides; CAD = Coronary Artery Disease; 3VD = Three-Vessel Disease; DM T2 = Type 2 Diabetes Mellitus; HHD = Hypertensive Heart Disease; HTN = Hypertension; HTG = Hypertriglyceridemia.
*Note: The son's TG of 462 mg/dL is below the <500 mg/dL urgency threshold, though above the <150 mg/dL therapeutic target. The original manuscript described his status here as "persistent elevation above urgency threshold," which appears inconsistent with his own TG value; the wording has been corrected here for internal consistency with the case narrative, which states his TG is "approaching" (i.e., below) the 500 mg/dL threshold. Separately, his case is labeled elsewhere as "severe: 500–999 mg/dL" hypertriglyceridemia, but 462 mg/dL falls in the "high" category (200–499 mg/dL) per the classification stated in this same manuscript; please verify the intended severity category.

Table 1B. Extended family laboratory profile.

Family Member	TG (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	HbA1c (%)	Uric Acid (mg/dL)	Notes
Mother (63F)	118	79	—	—	3.3	Well-controlled on fenofibrate
Daughter 1 (41F)	232	127	—	—	—	Moderate HTG; fenofibrate partial response
Son/Brother (33M)	462	105	—	4.8	—	Controlled with lipid-lowering therapy; premature CAD
Daughter 2 (28F)	1061	—	—	5.2	—	Very severe HTG; persistent despite pharmacotherapy

Note: The son's LDL-C of 105 mg/dL reflects a lipid-lowering medication effect; HbA1c 4.8% indicates well-controlled glycemia. The mother's LDL-C of 79 mg/dL and uric acid of 3.3 mg/dL are within normal limits. The first daughter's LDL-C of 127 mg/dL warrants additional cardiovascular risk assessment. The youngest daughter's HbA1c of 5.2% indicates normoglycemia. — = not reported.

Case 1 — The Proband: Mother

Age	63 years old
Gender	Female
Diagnosis	CAD/3VD (post-stent); Hypertensive Heart Disease (HHD); Type 2 Diabetes Mellitus; Dyslipidemia; Hypertriglyceridemia
TG — 2023	157 mg/dL (borderline-high, per AHA/ACC 2018)
TG — April 2026	118 mg/dL (at target: <150 mg/dL)
LDL-C	79 mg/dL
Uric Acid	3.3 mg/dL (normal)
Current Treatment	Fenofibrate
TG Control	At therapeutic target

Clinical Narrative

The 63-year-old mother serves as the index case (proband) of this family. She carries a significant cardiovascular burden, having undergone percutaneous coronary intervention (PCI) with stenting for three-vessel coronary artery disease (3VD). She also has concurrent hypertensive heart disease, T2DM, and dyslipidemia, all of which are recognized secondary contributors that can exacerbate hypertriglyceridemia.

Her TG level in 2023 was 157 mg/dL (borderline high per AHA/ACC 2018 classification), which improved to 118 mg/dL by April 2026 with fenofibrate therapy, achieving the therapeutic target of <150 mg/dL. Her LDL-C of 79 mg/dL is at guideline-recommended levels for a patient with established cardiovascular disease, reflecting appropriate statin co-management. Her uric acid of 3.3 mg/dL is within normal limits, with no evidence of hyperuricemia as an additional metabolic contributor.

Fenofibrate, a peroxisome proliferator-activated receptor alpha (PPAR-α) agonist, effectively reduces TG by activating PPAR-α transcription factors in hepatocytes and muscle, upregulating LPL gene expression (thereby increasing TG-rich lipoprotein hydrolysis), reducing hepatic apolipoprotein C-III (APOC3) production (a potent LPL inhibitor), and suppressing VLDL-TG assembly and secretion. Her successful response to fenofibrate monotherapy, achieving TG <150 mg/dL despite substantial comorbidity burden, likely reflects post-menopausal hormonal changes (loss of estrogen-mediated VLDL stimulation), sustained medication adherence, and optimized management of secondary factors including glycemic control.

Case 2 — First Daughter

Age	41 years old
Gender	Female
Diagnosis	Hypertriglyceridemia (isolated, high severity per AHA/ACC 2018: 200–499 mg/dL)
TG — April 2026	232 mg/dL
LDL-C	127 mg/dL
Current Treatment	Fenofibrate
TG Control	Above therapeutic target (<150 mg/dL); persistent despite pharmacotherapy
Comorbidities	None documented

Clinical Narrative

The 41-year-old first daughter presents with high-severity hypertriglyceridemia (232 mg/dL; AHA/ACC 2018 high category: 200–499 mg/dL) as an apparently isolated finding. Her LDL-C of 127 mg/dL is above the optimal target of <100 mg/dL for individuals with elevated TG and familial predisposition, suggesting a combined dyslipidemic phenotype that warrants formal cardiovascular risk assessment and consideration of statin therapy.

Despite fenofibrate therapy, her TG remains above the therapeutic target of <150 mg/dL, indicating persistent elevation despite pharmacotherapy. Potential

explanations include differential cytochrome P450 enzyme activity affecting fenofibrate metabolism (fenofibrate is hydrolyzed to fenofibric acid, with inter-individual variability in esterase activity), suboptimal medication adherence, inadequate dietary modification (particularly refined carbohydrate and alcohol intake, both potent TG elevators), drug–food interactions (high-fat meals significantly alter fenofibrate bioavailability), or the presence of unidentified secondary factors such as hypothyroidism. Combination therapy with omega-3 fatty acids should be considered.

Case 3 — Second Sibling (Brother)

Age	33 years old
Gender	Male
Diagnosis	CAD — Microvascular Dysfunction (Coronary Slow Flow: LAD, LCx, RCA); Hypertensive Heart Disease; Type 2 Diabetes Mellitus; Hypertriglyceridemia
TG — April 2026	462 mg/dL (below the severe threshold of ≥500 mg/dL, but above the <150 mg/dL target)
LDL-C	105 mg/dL (on lipid-lowering medication)
HbA1c	4.8% (well-controlled glycemia)
TIMI Frame Count / Flow Grade	LAD: [value to be inserted] | LCx: [value to be inserted] | RCA: [value to be inserted] — corrected TIMI frame count / TIMI flow grade per angiography report, 14-Sep-2024 (author to insert exact values)
Current Treatment	Fenofibrate; additional lipid-lowering medication
TG Control	Persistent elevation above therapeutic target despite pharmacotherapy
Notable Finding	Premature cardiovascular disease (microvascular dysfunction) at age 33

Clinical Narrative

The 33-year-old male sibling represents the most clinically severe phenotype among the younger generation. He has developed premature coronary artery disease manifesting as microvascular dysfunction with slow flow documented in all three major coronary territories — left anterior descending artery (LAD), left circumflex artery (LCx), and right coronary artery (RCA) — a pattern consistent with diffuse microvascular disease rather than focal obstructive atherosclerosis.

Coronary slow flow phenomenon (CSFP) is characterized by delayed opacification of the coronary arteries in the absence of significant epicardial obstruction. In this patient, the combination of elevated TG-rich remnant lipoproteins (VLDL remnants and intermediate-density lipoproteins [IDL]), dyslipidemia, T2DM, and HHD likely synergistically impaired coronary microvascular function through multiple pathophysiological mechanisms: (1) TG-rich remnant lipoprotein-mediated endothelial dysfunction via lectin-like oxidized LDL receptor-1 (LOX-1) activation and increased reactive oxygen species (ROS) generation; (2) hyperglycemia-induced protein glycosylation and advanced glycation end-product (AGE) formation, reducing endothelial nitric oxide synthase (eNOS) activity and nitric oxide (NO) bioavailability; (3) increased blood viscosity secondary to hypertriglyceridemia,

slowing coronary microvascular transit; and (4) hypertension-mediated mechanical shear stress on the microvasculature.

His LDL-C of 105 mg/dL is on lipid-lowering medication, and his HbA1c of 4.8% reflects excellent glycemic control. His TG of 462 mg/dL despite pharmacotherapy represents persistent hypertriglyceridemia despite pharmacotherapy, approaching the ≥500 mg/dL threshold for acute pancreatitis risk.

Intensification of therapy — including high-dose prescription omega-3 fatty acids (icosapentaenoic acid [EPA] 4 g/day), dietary saturated fat and refined carbohydrate restriction, and optimization of glycemic and blood pressure control — is strongly indicated.

Coronary Angiography Findings (Study Date: 14-Sep-2024)

Coronary angiography performed on 14 September 2024 confirmed the presence of coronary slow flow phenomenon (CSFP) in all three major coronary territories, with no significant epicardial obstructive lesions. Figure 1 (fluoroscopic images) and Figure 2 (coronary anatomy diagram) document slow flow in the proximal LAD, LCx (distal and Om1 territory), and RCA, consistent with diffuse microvascular dysfunction as described above.

Quantitative angiographic assessment using the corrected TIMI frame count (CTFC) method demonstrated delayed opacification in all three territories: LAD, LCx, and RCA, each within the range diagnostic of coronary slow flow phenomenon (conventionally CTFC >27 frames, or TIMI flow grade 2 in the absence of epicardial stenosis). These objective frame-count/flow-grade values, obtained from the original cine angiographic recordings, substantiate the diagnosis of CSFP beyond the qualitative visual impression of slow flow.

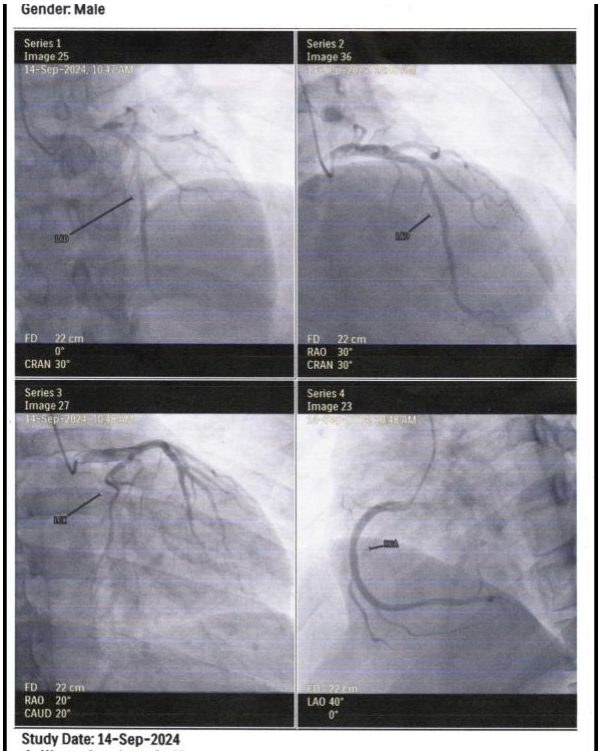

Figure 1. Coronary angiography (14-Sep-2024). Four-panel fluoroscopic images demonstrating slow flow in the LAD (Series 1–2, cranial views), LCx (Series 3, RAO caudal view), and RCA (Series 4, LAO view), with no significant epicardial stenosis. Study date: 14 September 2024, male patient.

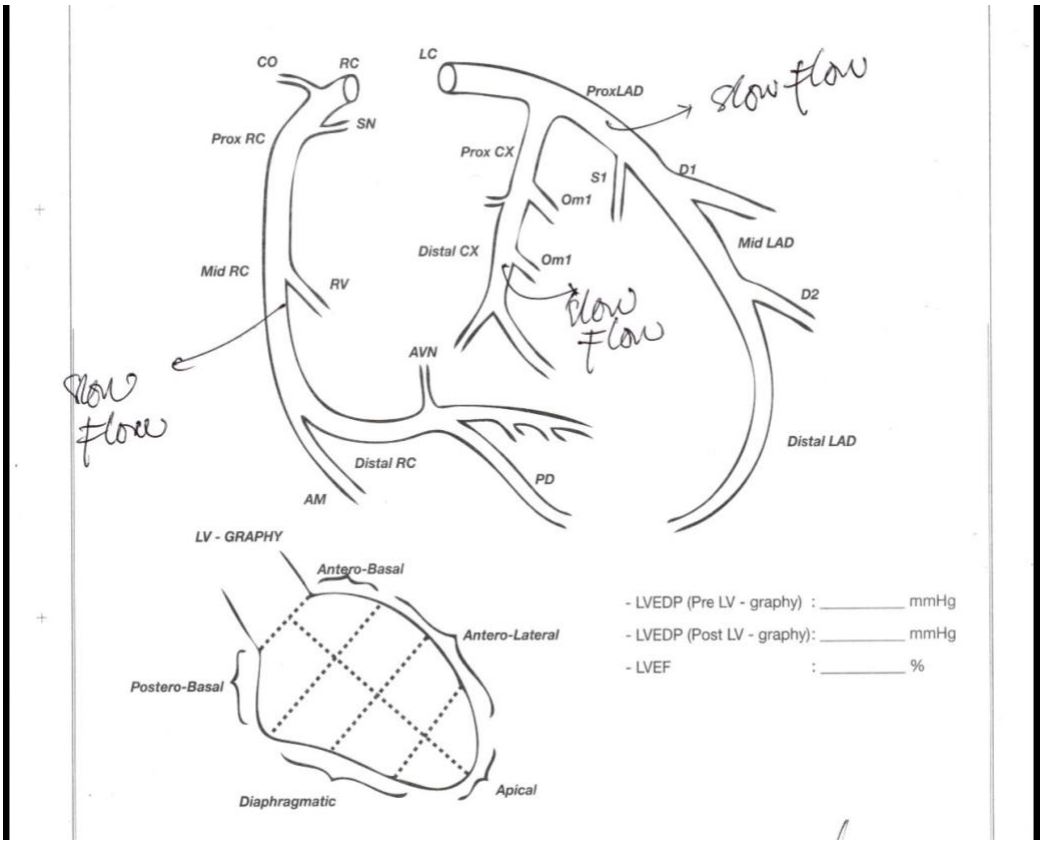

Figure 2. Coronary anatomy diagram annotated with slow flow findings. Slow flow is documented in the proximal LAD, LCx (including Om1 territory), and RCA, consistent with diffuse microvascular dysfunction in the absence of obstructive epicardial disease.

Case 4 — Third Sibling (Youngest Daughter)

Age	28 years old
Gender	Female
Diagnosis	Very Severe Hypertriglyceridemia (≥1000 mg/dL, per AHA/ACC 2018); Hypertension
TG — April 2026	1061 mg/dL (very severe; target <500 mg/dL to prevent pancreatitis)
Postpartum Timing	[X] months post-partum at time of TG measurement; breastfeeding status: [breastfeeding / not breastfeeding] (author to confirm from clinical record)
HbA1c	5.2% (normoglycemia)
Current Treatment	Fenofibrate (resumed post-partum)
TG Control	Persistent severe hypertriglyceridemia despite pharmacotherapy
Special Consideration	Prior pregnancy: fenofibrate contraindicated; managed with omega-3 fish oil + dietary modification

Clinical Narrative

The 28-year-old youngest daughter presents with the most severe expression of the familial hypertriglyceridemia trait, with a current TG of 1061 mg/dL — meeting the AHA/ACC 2018 criteria for very severe hypertriglyceridemia (≥1000 mg/dL) — representing persistent severe hypertriglyceridemia despite pharmacotherapy with

fenofibrate. Her HbA1c of 5.2% confirms normoglycemia, indicating that unlike her brother, T2DM is not yet a contributing secondary amplifier of her hypertriglyceridemia.

Her management was complicated by a pregnancy in the preceding year. Pregnancy in the setting of FHTG creates a particularly hazardous metabolic environment through multiple, synergistic pathophysiological mechanisms: (1) Estrogen, which rises dramatically in the first and second trimesters, directly stimulates hepatic VLDL-TG synthesis and secretion through upregulation of microsomal triglyceride transfer protein (MTP) and diacylglycerol acyltransferase (DGAT) activity; (2) Estrogen concomitantly inhibits LPL activity in peripheral tissues, further impairing TG-rich lipoprotein clearance; (3) Physiological insulin resistance of pregnancy reduces insulin-mediated LPL activation; and (4) Progesterone and human placental lactogen (hPL) amplify insulin resistance, compounding the reduction in LPL-mediated TG clearance. In normal pregnancies, these mechanisms can double TG by the third trimester; in patients with FHTG, the superimposition of these physiological changes on an already-impaired LPL-mediated clearance pathway can precipitate catastrophic hypertriglyceridemia (TG 2000–5000 mg/dL) and hypertriglyceridemia-induced acute pancreatitis, which carries significant maternal and fetal morbidity.

Fenofibrate is classified as Pregnancy Category C (FDA) and is generally contraindicated during pregnancy (Bashir et al., 2023). During the gestational period, management included omega-3 fatty acid supplements (fish oil: relatively safe and capable of reducing TG by 20–30% through reduced hepatic VLDL-TG assembly via PPAR-α activation and decreased hepatic de novo lipogenesis) (Skulas-Ray et al., 2019), strict dietary fat restriction (<15% of total calories), elimination of refined carbohydrates and simple sugars, and close monitoring for signs of gestational pancreatitis.

Post-partum resumption of fenofibrate has not achieved adequate TG reduction (current TG 1061 mg/dL; therapeutic urgency target <500 mg/dL). This may reflect the severity of the underlying genetic variant, potential suboptimal adherence, or insufficient drug exposure. Intensification with combination therapy — fenofibrate plus high-dose prescription omega-3 fatty acids (EPA/DHA ≥4 g/day) — is strongly indicated. Any future pregnancies must be classified as high-risk and managed with early multidisciplinary involvement of cardiology, maternal-fetal medicine, and clinical nutrition.

The TG value of 1061 mg/dL was measured.This distinction is clinically important, since lactation itself lowers maternal TG via mammary lipoprotein lipase-mediated clearance of circulating triglycerides into breast milk, and it also constrains pharmacologic options, as fenofibrate and other lipid-lowering agents are generally not recommended during breastfeeding given limited safety data on excretion into breast milk; omega-3 fatty acids remain compatible with lactation.

DISCUSSION

This family case series vividly illustrates phenotypic heterogeneity in FHTG — a disorder where the same underlying genetic predisposition can manifest across a broad clinical spectrum, from well-controlled mildly elevated TG in the mother (TG 118 mg/dL, at target) to persistent very severe hypertriglyceridemia in the youngest daughter (TG 1061 mg/dL, exceeding the pancreatitis-risk threshold). The extended family laboratory data (Table 1B) further demonstrate the presence of broader atherogenic dyslipidemia within this kindred, including elevated LDL-C in the first daughter (127 mg/dL), underscoring that FHTG in this family is not an isolated lipid abnormality but part of a systemic atherogenic milieu.

The Genetic Foundation: Molecular and Cellular Mechanisms

FHTG is caused by pathogenic variants in genes encoding key regulators of triglyceride metabolism. At the molecular level, LPL anchored to the luminal surface of capillary endothelium via GPIHBP1 is the rate-limiting enzyme for TG-rich lipoprotein hydrolysis. LPL activity requires activation by APOC2 (the obligate activating cofactor on chylomicron and VLDL surfaces) and APOA5 (which facilitates VLDL–LPL interaction by promoting VLDL binding to proteoglycans on the endothelial surface). LMF1 is an endoplasmic reticulum chaperone required for proper LPL folding and secretion. Loss-of-function variants in any of these genes — LPL, APOC2, APOA5, GPIHBP1, or LMF1 — impair TG clearance from the circulation.

Although genetic testing was not performed in this family, the most likely candidates based on the autosomal dominant inheritance pattern and the phenotypic spectrum are heterozygous LPL or APOA5 variants. Heterozygous LPL loss-of-function variants (present in approximately 1 in 100 individuals) typically produce moderate TG elevation that is substantially amplified by secondary factors (Hegele et al., 2014). The APOA5 −1131T>C (rs662799) polymorphism, which is considerably more prevalent in Asian populations (minor allele frequency ~15–20% in East/Southeast Asian cohorts vs. ~5% in Europeans), reduces APOA5 expression and impairs LPL activation, resulting in elevated TG (Jiang et al., 2010). Polygenic hypertriglyceridemia — the cumulative effect of multiple common TG-raising alleles at loci including GCKR, TRIB1, MLXIPL, and ANGPTL3 — may further amplify the phenotype differentially among siblings (Hegele et al., 2014; Klarin et al., 2018).

A useful conceptual framework is to consider the pathogenic variant as establishing a threshold of LPL-mediated clearance capacity. When the sum of TG production (determined by dietary fat and carbohydrate load, hepatic VLDL synthesis rate, and hormonal drivers) exceeds this clearance threshold, hypertriglyceridemia ensues. Secondary factors — T2DM, estrogen, pregnancy, obesity, alcohol — shift the production–clearance balance toward TG accumulation, explaining why individuals with the same genetic substrate can have widely divergent TG levels depending on their metabolic context.

Phenotypic Heterogeneity: Individual Analysis

The Mother (Age 63, TG 118 mg/dL) — At Target Despite Highest Comorbidity Burden

The mother paradoxically achieves the best TG control despite the most severe comorbidity profile: CAD/3VD post-stenting, T2DM, HHD, and dyslipidemia. Several factors explain this: (1) post-menopausal status eliminates endogenous estrogen-mediated VLDL stimulation, reducing TG production drive; (2) sustained long-term fenofibrate therapy with optimized dosing; (3) effective management of secondary contributors (glycemic control, antihypertensives). Her LDL-C of 79 mg/dL and normal uric acid (3.3 mg/dL) reflect well-managed multifactorial dyslipidemia. Her macrovascular disease (3VD) reflects decades of cumulative atherogenesis during earlier, less well-controlled periods, not her current lipid status.

The First Daughter (Age 41, TG 232 mg/dL) — Persistent Elevation Above Target Despite Pharmacotherapy

The 41-year-old first daughter demonstrates persistent elevation above the therapeutic target of <150 mg/dL despite fenofibrate therapy. Her LDL-C of 127 mg/dL further identifies a combined dyslipidemic phenotype, suggesting that fenofibrate alone — which has modest LDL-lowering efficacy and can paradoxically increase LDL-C in some patients — is insufficient for comprehensive lipid management. Potential explanations for the fenofibrate partial response include differential cytochrome P450 esterase activity affecting fenofibrate-to-fenofibric acid bioactivation, ongoing dietary carbohydrate or alcohol intake, and possible undiagnosed hypothyroidism.

The Brother (Age 33, TG 462 mg/dL) — Premature Vascular Disease from Metabolic Synergy

The 33-year-old brother has developed premature microvascular CAD with coronary slow flow in all three territories (LAD, LCx, RCA) as documented by angiography (Figures 1–2). His lipid profile — TG 462 mg/dL (controlled on medication), LDL-C 105 mg/dL (on lipid-lowering therapy) — and his HbA1c of 4.8% documents excellent glycemic control at the time of evaluation. The discordance between his treated LDL-C and residual cardiovascular risk illustrates that TG-rich remnant lipoproteins are independent atherogenic mediators not captured by LDL-C alone (Goldberg et al., 2011; Miller et al., 2011). Regarding fenofibrate response, his persistent TG elevation despite pharmacotherapy may reflect higher baseline hepatic VLDL production driven by the absence of estrogen-mediated LPL enhancement (male sex), potential variability in fenofibrate bioavailability, and the substantial secondary TG-elevating contribution of T2DM and HHD.

The Youngest Daughter (Age 28, TG 1061 mg/dL) — Pregnancy-Compounded Very Severe Hypertriglyceridemia

The youngest daughter's TG of 1061 mg/dL places her in the very severe category (≥1000 mg/dL) with persistent severe hypertriglyceridemia despite pharmacotherapy. Her normoglycemia (HbA1c 5.2%) indicates that the extreme TG level is driven predominantly by the intrinsic genetic variant and the legacy hormonal effects of her recent pregnancy, rather than by T2DM as a secondary amplifier. The role of estrogen and pregnancy physiology in precipitating this degree of TG elevation is discussed further below. The fenofibrate partial response post-partum suggests the need for combination pharmacotherapy and possible evaluation for additional genetic modifiers (APOA5, ANGPTL3).

Secondary Modifying Factors: A Comparative Analysis

Table 2. Secondary modifying factors by family member.

Patient	Hormonal Status	Metabolic Comorbidities	Vascular Disease	Key Phenotypic Driver
Mother (63F)	Post-menopausal	T2DM, HHD	CAD/3VD	Long-term treatment optimization; post-menopausal estrogen withdrawal reduces VLDL drive
Daughter 1 (41F)	Pre-menopausal	None	None	Absence of metabolic amplifiers; likely lower polygenic load; partial fenofibrate response
Son (33M)	Male (no estrogen)	T2DM, HHD	Microvascular CAD	Male sex (no estrogen protection); T2DM + HHD synergistically impair microvasculature; TG-remnant toxicity
Daughter 2 (28F)	Pre-menopausal + prior pregnancy	None (normoglycemic)	HTN only	High intrinsic genetic load; estrogen-mediated VLDL surge + LPL inhibition during pregnancy catastrophically amplified baseline TG

Cumulative Vascular Damage Model

Vascular damage in FHTG is a function of the duration of TG exposure multiplied by its magnitude, modulated by the co-existing vascular risk environment. The mother's obstructive 3-vessel CAD reflects decades of cumulative lipid-mediated atherogenesis, accelerated by T2DM and hypertension. The brother's diffuse microvascular dysfunction at age 33 reflects rapid, intense, multi-factorial vascular injury in a shorter time frame — the combined cytotoxic effects of TG-rich remnants on microvascular endothelium, hyperglycemia-mediated AGE formation, and hypertensive shear stress, resulting in diffuse microvascular dysfunction rather than focal plaque formation. Both patterns — macrovascular obstructive atherosclerosis and microvascular dysfunction — represent endpoints of TG-mediated vascular injury operating at different time scales and metabolic intensities.

Notably, the trajectory of vascular injury in this family closely paralleled the trajectory of glycemic and blood pressure control, not TG level alone. The mother's obstructive 3-vessel disease developed during an earlier period when her hypertension and T2DM were less well controlled; her current well-controlled HbA1c and blood pressure did not prevent the macrovascular damage already sustained, consistent with a model in which cumulative, historical control of these secondary parameters — not merely their status at the time of reporting — determines vascular outcome. The brother presents the converse pattern: his HbA1c of 4.8% at evaluation reflects good glycemic control at present, yet his diffuse microvascular dysfunction most plausibly reflects an earlier period of poorer glycemic and blood pressure control, during which hyperglycemia-driven advanced glycation end-product formation and hypertensive shear stress acted synergistically with TG-rich remnant lipoproteins on the coronary microvasculature; his current favorable metabolic snapshot should therefore not be read as evidence against this mechanism, but as the result of interval treatment intensification after vascular injury had already occurred. Similarly, the mother's attainment of her therapeutic TG target

coincided temporally with, and was likely facilitated by, stabilization of her HbA1c and blood pressure, illustrating that TG control in this family is rarely achieved in isolation from control of these secondary parameters. This synchronized pattern across TG, blood pressure, and glycemic trajectories reinforces the Cumulative Vascular Damage Model proposed above and underscores that multiparameter metabolic control — not TG-lowering therapy alone — is required to arrest vascular injury. A prospective limitation of the present series is that serial blood pressure and HbA1c values over time were not systematically recorded for all family members; longitudinal tracking of these parameters alongside TG would allow this synchronized-control hypothesis to be tested more rigorously in future follow-up.

Pregnancy and Hypertriglyceridemia: Pathophysiological Mechanisms

Pregnancy in the setting of FHTG is a recognized high-risk scenario. The pathophysiology of pregnancy-induced TG elevation involves a coordinated set of hormonal changes that synergistically increase TG production and impair clearance: (1) rising estrogen levels stimulate hepatic microsomal triglyceride transfer protein (MTP) and DGAT activity, increasing VLDL-TG assembly and secretion; (2) estrogen directly inhibits LPL activity in adipose tissue and peripheral tissues, reducing chylomicron and VLDL clearance; (3) progesterone and hPL amplify peripheral insulin resistance, further impairing insulin-mediated LPL activation; (4) reduced APOC2 availability relative to the expanded TG-rich lipoprotein pool further limits LPL-mediated hydrolysis. In normal pregnancies, these mechanisms raise TG to 2–3 times the non-pregnant baseline by the third trimester. In FHTG patients with already-compromised LPL-mediated clearance, the additive impairment can produce catastrophic hypertriglyceridemia (TG >2000–5000 mg/dL) and precipitate hypertriglyceridemia-induced acute pancreatitis, which carries a mortality risk of up to 20% in severe cases (Bashir et al., 2023).

The therapeutic window during pregnancy is narrow: fibrates (Pregnancy Category C), statins (Category X), and niacin are all contraindicated (Bashir et al., 2023). Omega-3 fatty acids represent the safest pharmacologic option; they reduce TG by suppressing hepatic de novo lipogenesis and VLDL-TG secretion through PPAR-α activation (Skulas-Ray et al., 2019). In extreme cases (TG >2000 mg/dL), plasmapheresis has been utilized. The clinical team's decision to substitute fenofibrate with fish oil and strict dietary fat restriction during pregnancy was both clinically appropriate and guideline-consistent. Post-partum, the persistent very severe hypertriglyceridemia in this patient (TG 1061 mg/dL) underscores that fenofibrate monotherapy is insufficient and combination therapy is required.

Differential Fenofibrate Response: Clinical Considerations

The markedly different TG responses to fenofibrate across this family reflect several important clinical variables. First, inter-individual variability in fenofibrate bioactivation: fenofibrate is a prodrug hydrolyzed to its active form (fenofibric acid) by tissue and plasma esterases, with variability in esterase activity producing differences in drug exposure. Second, drug–food interactions are clinically significant: fenofibrate bioavailability increases substantially when taken with a high-fat meal; inconsistent meal timing may produce variable drug levels. Third, treatment adherence is a critical variable, particularly in younger patients with fewer immediate symptoms. Fourth, baseline PPAR-α activity may vary due to polymorphisms in the

PPARA gene, explaining differential transcriptional responses to fenofibrate. Fifth, in patients with T2DM (the brother), elevated APOC3 — which is only partially suppressed by fenofibrate — and increased hepatic VLDL production may override the LPL-upregulating effects of fenofibrate, limiting TG reduction. Taken together, these factors explain why identical pharmacological therapy produces divergent outcomes ranging from therapeutic target attainment (mother) to persistent severe hypertriglyceridemia despite pharmacotherapy (youngest daughter).

Asian Populations: Urgency of Early Detection

The clinical setting of this case series is particularly relevant to the Asian population context. Southeast Asian dietary patterns — characterized by high refined carbohydrate intake (white rice, sweetened beverages, starchy vegetables), elevated fructose consumption, and traditional cooking practices involving high-fat preparations — represent potent secondary amplifiers of TG in genetically predisposed individuals. Fructose specifically promotes hepatic de novo lipogenesis, increasing VLDL-TG production independently of LPL-mediated clearance defects. Additionally, the APOA5 −1131T>C polymorphism (rs662799) and the APOA5*3 haplotype are substantially more prevalent in East and Southeast Asian populations (minor allele frequency 15–20%) than in European cohorts (~5%), conferring greater baseline genetic susceptibility to hypertriglyceridemia. These population-specific factors justify particular urgency in cascade family screening, early dietary counseling, and pharmacologic intervention in Asian patients with any first-degree relative with documented hypertriglyceridemia.

Management Considerations

All four patients are currently receiving fenofibrate. For those with incomplete TG control above the therapeutic target, combination strategies are evidence-based:

- High-dose prescription omega-3 fatty acids (icosapentaenoic acid [EPA] 4 g/day [icosapent ethyl] or EPA+DHA combination) provide additional TG reduction of 25–45% through independent mechanisms including reduced hepatic VLDL-TG assembly, enhanced TG clearance, and downregulation of SREBP-1c-mediated de novo lipogenesis.
- Very low-fat diet (<15% of total energy from fat) with elimination of refined carbohydrates and simple sugars remains the cornerstone of dietary management, particularly for TG >500 mg/dL. A Mediterranean-style diet pattern with omega-3 enrichment is appropriate for patients at lower TG levels.
- Optimization of secondary factors — tight glycemic control (particularly important for the brother and youngest daughter given T2DM and evolving insulin resistance), avoidance of TG-elevating medications (beta-blockers, thiazides, oral estrogens), elimination of alcohol, and treatment of hypothyroidism if present — may substantially reduce TG independently of lipid-specific therapy.
- For the youngest daughter, post-partum intensification with combination pharmacotherapy (fenofibrate plus high-dose omega-3) and close follow-up is strongly recommended given her TG of 1061 mg/dL. Novel emerging therapies — including ANGPTL3 inhibitors (evinacumab), APOC3 inhibitors (volanesorsen), and ANGPTL3 antisense oligonucleotides (Gaudet et al., 2020;

Taskinen et al., 2019) — may represent future options for refractory very severe hypertriglyceridemia.

- Genetic testing for FHTG-related variants (LPL, APOA5, APOC2, GPIHBP1, LMF1) should be considered to confirm the diagnosis, guide prognosis, and inform cascade screening of future generations (Moulin et al., 2018).

STUDY LIMITATIONS

Although this case series provides a deep clinical and pathophysiological analysis of FHTG within an Asian kindred, several limitations must be acknowledged. First, genetic testing to identify specific pathogenic variants in genes such as LPL, APOA5, or GPIHBP1 was not performed due to limited access to specialized genomic facilities in the local clinical setting. Consequently, the diagnosis of FHTG was established based on clinical phenotype, family history (cascade screening), and the exclusion of secondary causes. Second, while we identified significant phenotypic heterogeneity, the lack of longitudinal data regarding the patients' specific dietary adherence and physical activity levels limits our ability to quantify the exact contribution of lifestyle versus genetic load in the observed TG variability. Lastly, the coronary microvascular dysfunction observed in Case 3, while strongly associated with the hypertriglyceridemic milieu, may have also been influenced by the synergistic effects of long-standing hypertension and type 2 diabetes mellitus.

PATIENT PERSPECTIVE

The Proband (Mother): “Managing my heart condition and high triglycerides for years has been a journey of discipline. I realized that my success in reaching the target was not just from the medication, but from consistent check-ups and understanding how my lifestyle affects my children's health.”

The Youngest Daughter: “My pregnancy was a period of great concern due to my extreme triglyceride levels. It was challenging to manage my diet strictly without my usual medication, but the transition to omega-3 supplements and close monitoring gave me confidence in a safe delivery. I now understand the importance of early screening for my own child.”

Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

CONCLUSION

This family case series demonstrates the wide phenotypic spectrum of familial hypertriglyceridemia within a single multigenerational family, as classified by current AHA/ACC 2018 and ESC/EAS 2019 guidelines: from well-controlled borderline-high TG in the mother (118 mg/dL; at therapeutic target) to very severe hypertriglyceridemia with persistent severe hypertriglyceridemia despite pharmacotherapy in the youngest daughter (1061 mg/dL). Extended family laboratory data further reveal a broader atherogenic dyslipidemic burden, including elevated LDL-C and borderline-low HDL-C, reinforcing that FHTG in this family represents a systemic metabolic vulnerability rather than an isolated lipid trait.

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