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Original Research

The longitudinal triglyceride phenotype in heterozygotes with *LPL* pathogenic variants

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KEYWORDS
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Lipoprotein lipase deficiency;
Next-generation DNA sequencing;
Pathogenic variant

Background: Biallelic pathogenic variants in lipoprotein lipase (LPL) cause familial chylomicronemia syndrome with severe hypertriglyceridemia (HTG), defined as plasma triglycerides (TG) > 10 mmol/L (> 885 mg/dL). TG levels in individuals with one copy of a pathogenic *LPL* gene variant is less familiar; some assume that the phenotype is intermediate between homozygotes and controls.

Objective: We undertook an evaluation of the longitudinal TG phenotype of individuals heterozygous for pathogenic *LPL* variants.

Methods: Medically stable outpatients were evaluated based on having: (1) a single copy of a rare pathogenic *LPL* variant; and (2) serial fasting TG measurements obtained over > 1.5 years of follow-up.

Results: Fifteen patients with a single pathogenic *LPL* variant were followed for a mean of 10.3 years (range 1.5 to 30.3 years). TG levels varied widely both within and between patients. One patient had normal TG levels < 2.0 mmol/L (< 175 mg/dL) continuously, while four patients had at least one normal TG level. Most patients fluctuated between mild-to-moderate and severe HTG: five patients had only mild-to-moderate HTG, with TG levels ranging from 2.0 to 9.9 mmol/L (175 to 885 mg/dL), while 6 patients had at least one instance of severe HTG. Of the 203 total TG measurements from these patients, 14.8%, 67.0% and 18.2% were in the normal, mild-to-moderate and severe HTG ranges, respectively.

Conclusion: The heterozygous LPL deficient phenotype is highly variable both within and between patients. Heterozygosity confers susceptibility to a wide range of TG phenotypes, with severity likely depending on secondary factors.

Introduction

Hypertriglyceridemia (HTG) – i.e. elevated fasting plasma triglyceride (TG) concentration – is commonly encountered clinically.[1,2] One quarter of North Americans display mild-to-moderate HTG, defined as TG levels between 2.0 to 9.9 mmol/L (175 to 885 mg/dL)

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while one in 400 individuals display severe HTG, defined as TG levels > 10 mmol/L (> 885 mg/dL).[2] Severe HTG in adults is associated with increased risk of acute pancreatitis and atherosclerotic cardiovascular disease (ASCVD). [1]

Familial chylomicronemia syndrome (FCS) is an ultrarare phenotype, with prevalence estimated at one in 100,000 to 1,000,000.[3–5] FCS is caused by biallelic pathogenic variants in the *LPL* gene encoding lipoprotein lipase (LPL) or in one of four other genes encoding LPL-interacting proteins, specifically *APOC2, APOA5, GPIHBP1* and *LMF1* encoding apolipoprotein (apo) C-II, apo A-V, glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1 (GPIHBP1) and lipase maturation factor 1 (LMF1), respectively.[6] FCS is characterized by sustained refractory HTG and systemic manifestations including lipemia retinalis, eruptive xanthomatosis and hepatosplenomegaly. About 80% of FCS cases are caused by biallelic pathogenic variants in *LPL* (synonymous with LPL deficiency or former Fredrickson hyperlipoproteinemia type 1), with the remaining cases resulting from biallelic variants in the other four genes.[6]

The phenotype of FCS - and specifically LPL deficiency - has been well studied over the past 50 years. However, the phenotype resulting from the more common situation of a single copy of pathogenic variant in *LPL* (i.e. heterozygous LPL deficiency) is less familiar and has been less systematically evaluated.[4] Some physicians have extrapolated the clinical expression of heterozygous LPL deficiency from the pattern observed in autosomal dominant familial hypercholesterolemia (FH), in which untreated heterozygotes display a fully expressed, stable phenotype that is about half as severe as in homozygotes.[7] However, the biology of the mutated cell surface receptor in FH does not automatically provide an appropriate model for the mutated plasma enzyme in LPL deficiency. Does phenotypic expression of pathogenic *LPL* variants follow the FH model? In other words, do heterozygotes have an abnormal phenotype that is intermediate in severity between a homozygous, healthy individual with two normal alleles? Furthermore, is the phenotype of heterozygotes stable over time?

We previously showed that heterozygotes for rare, pathogenic variants in *LPL* are significantly overrepresented – by 3- to 4-fold – in cohorts with both severe and mild-to-moderate HTG, but are also present in a small proportion (∼3%) of adults with normal TG levels.[8,9] The wide range of TG phenotypes suggests that the analogy with heterozygous FH might be inappropriate. Here, we evaluated TG levels in individuals heterozygous for pathogenic *LPL* variants who were followed for years. We found that the TG phenotypes were highly variable both within and between patients, ranging from normal to severe HTG, at baseline and longitudinally.

Methods

Study subjects

Individuals were patients at the Lipid Genetics Clinic, London, Ontario, Canada who were referred for management of their lipid levels. Inclusion criteria were: (1) heterozygosity for a pathogenic *LPL* variant; (2) at least three TG measurements taken over a minimum of 1.5 years; and (3) patient was medically stable over the duration of follow-up. The project was approved by the Research Ethics Board of Western University (protocol number 0379) and all participants provided informed consent.

Biochemical, clinical and demographic information

As part of routine lipid profiling after an 8 to 12 hour fasting period, plasma TG measurements were collected for all patients at baseline and at routine follow-up visits to the Lipid Genetics Clinic. Additional historical fasting plasma TG measurements were collected from referral notes provided to us at each patient's initial visit to the Lipid Genetics Clinic. Lipid profiles were measured using the Roche Cobas C502 Analyzer (Hoffmann La Roche, Mississauga, ON, Canada), as reported previously.[8,9] Clinical and demographic data were collected at the time of initial visit to the Lipid Genetics Clinic.

DNA preparation and sequencing

Genomic DNA isolation and gene sequencing protocols have been described previously.[8,10,11] Briefly, genomic DNA from whole blood was enriched for our LipidSeq panel, targeting 69 genes and 185 single nucleotide polymorphisms (SNPs) associated with dyslipidemia and other metabolic disorders.[12] Sequencing was performed using standard protocols at the London Regional Genomics Centre on a MiSeq personal sequencer (Illumina, San Diego CA).

Genetic analysis

Our standard bioinformatic processing and annotation pipeline was used to call variants.[8] Briefly, CLC Bio Genomics Workbench (version 12.0; CLC Bio, Aarhus, Denmark) was first used to align sequencing reads for each patient sample against the human reference genome (build hg19) and was then used to call variants.

Variant pathogenicity classification

Pathogenicity of *LPL* variants was first determined using the VarSome ACMG tool (https://varsome.com/about/resources/acmg-implementation/). In 2015, the American College of Medical Genetics and Genomics (ACMG) established a system for interpreting the pathogenicity of

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sequence variants.[13] The VarSome ACMG tool was developed to computerize this system originally designed for manual use by experienced clinicians. VarSome served as the first filter to identify pathogenic or likely pathogenic variants. We manually confirmed the pathogenicity of each variant using ACMG guidelines, resulting in a cohort of patients whom we were confident were heterozygous carriers of rare pathogenic *LPL* variants. For patients included in our study, pathogenic rare variants were only found in *LPL* and none of the other canonical FCS genes (i.e. *APOC2, APOA5, GPIHBP1* and *LMF1*).

Statistical analysis

Calculation of means and standard deviations was performed using GraphPad Prism 9.3.1 for Windows (GraphPad Software, San Diego, California USA, www.graphpad.com). Means are reported as mean ± standard deviation. Figures were generated in R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org/) using the ggplot2.[14]

Results

Study subjects

The filtering algorithm for patient inclusion is shown in Supplementary Fig. 1. Forty patients were heterozygous for a rare *LPL* variant. Of these, 19 were identified by the VarSome ACMG tool as having a pathogenic or likely pathogenic variant in *LPL*. Upon manual curation of variants in these 19 patients, two were excluded from further analysis as manual review concluded that variants possessed by those patients were variants of uncertain significance, not pathogenic or likely pathogenic. Two more patients were excluded due to an insufficient number of TG measurements available for review. Our final cohort consisted of 15 unrelated patients with pathogenic *LPL* variants (Supplementary Table 1).

Baseline demographic information

Demographic information and lipid-related clinical characteristics of our cohort are summarized in Table 1. Mean age and body mass index (BMI) were 48.1 ± 7.1 years and 30.2 ± 3.8 kg/m^2 respectively. Two subjects were of non-Northern European ancestry, two each had a history of pancreatitis and ASCVD, four had well-controlled type 2 diabetes. Over the duration of follow-up, no patient developed new-onset diabetes, or thyroid, renal or liver disease. In addition, medication use, including the use of lipid-lowering medications, was stable over the duration of follow-up. Only three patients were female. Only one patient was < 40 years of age and his baseline TG was 8.19 mmol/L. Only three patients had BMI < 27 kg/m^2 and their TG levels were 1.50, 2.03 and 3.70 mmol/L. Over the study duration, BMI remained stable for most patients. Over the duration of the study, 14 patients were continuously on a statin, 12 also took a fibrate, one took niacin, 4 took ezetimibe and 4 took over the counter omega-3 fatty acids. Prescriptions and dosages were consistent over > 90% of study visits and compliance was judged as satisfactory for all study participants.

Table 1 Baseline characteristics in patients heterozygous for pathogenic *LPL* variants.

Number of patients/females	15/3
Age (years)	48.1 ± 7.1
Body mass index (kg/m^2)	30.2 ± 3.8
Non-Northern European ancestry	2
Type 2 diabetes mellitus	4
History of acute pancreatitis	2
History of atherosclerotic cardiovascular disease	2
Current or former smoking history	5
No alcohol consumption	6
Total cholesterol (mmol/L)	7.36 ± 3.30
Triglycerides (mmol/L)	13.2 ± 14.1
High-density lipoprotein cholesterol (mmol/L)	0.66 ± 0.29

Values shown are mean ± standard deviation or number of patients (% of total cohort) unless otherwise indicated.

Pathogenic *LPL* variants

Six unique missense variants of *LPL* were found in our cohort: p.Val96Leu in two patients, p.Ala98Thr in one patient, p.Gly215Glu in five patients, p.Arg270Cys in two patients, p.Arg270His in one patient, and p.Val340Ile in one patient. One frameshift variant, p.Gln16fs, was found in two patients. One nonsense variant, p.Leu209Ter, was found in a single patient. All variants were previously reported, except p.Leu209Ter (Supplementary Table 1). The positions of each variant along the *LPL* gene are shown in Supplementary Fig. 2.

Variation in baseline triglycerides

At baseline, two (13.3%), seven (46.7%), and six (40%) patients had normal TG levels, mild-to-moderate HTG, and severe HTG, respectively. The average baseline lipid profile at initial visit to Lipid Genetics Clinic is shown in Table 1.

Distribution of longitudinal fasting plasma triglycerides in *LPL* heterozygotes

The average duration of follow-up was 10.3 ± 8.5 years. During follow-up, patients had on average 13 ± 8 TG measurements. Marked variability was observed in TG levels between patients at baseline (Fig. 1). Wide within-patient variability of TG levels over time was common: only one patient (6.7%) continuously had normal TG levels . Five patients (33.3%) had TG levels only within the mild-to-moderate HTG range continuously, while no patients had TG levels only within the severe HTG range. Six patients (40.0%) had

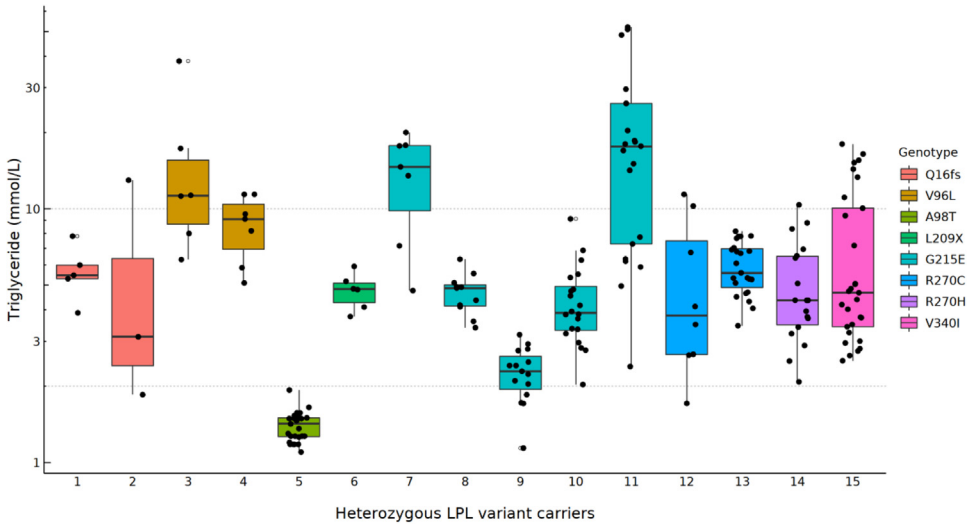

Fig. 1 Variable triglyceride phenotypes in patients heterozygous for pathogenic *LPL* variants. Distribution of longitudinal TG measurement data from heterozygous carriers of pathogenic *LPL* variants (N = 15) was graphed as individual box-and-whisker plots. Boxes are color-coded according to genotype. Each patient's median TG level is represented as the middle line of each box, while the whiskers display the interquartile range of triglycerides achieved by each patient. Individual TG measurements are represented as black dots. Fasting plasma TG (mmol/L) are displayed using a $\log_{10}$ scale. Horizontal lines at 2 and 10 mmol/L delineate the cut-offs for TG severity classifications (mild-to-moderate HTG is defined as TG between 2 and 9.9 mmol/L while severe HTG is TG > 10 mmol/L).

TG levels that fluctuated between mild-to-moderate and severe HTG ranges. TG levels in one patient (6.7%) fluctuated between normal and the mild-to-moderate HTG range, without entering the severe HTG range. Two patients (13.3%) had at least one TG reading in the normal, mild-to-moderate and severe HTG ranges at different time points. Among the 203 total TG measurements taken, 136 (67.0%) fell in the mild-to-moderate range, with the remainder divided between the normal and severe HTG ranges at 30 (14.8%) and 37 (18.2%), respectively.

Association between pathogenic *LPL* variants and longitudinal TG phenotype

No consistent pattern in longitudinal TG measurements was observed to be associated with a particular variant, and instead variability appeared to be a common feature of the heterozygotes for pathogenic *LPL* variants (Fig. 2). The five patients with the *LPL* p.Gly215Glu variant showed marked between-patient variability (Fig. 2E). There was phenotypic variability observed in carriers of other variants, such as p.Arg270Cys and p.Val96Leu (Fig. 2F and B, respectively).

Discussion

We report marked within and between patient variability of the TG phenotype in heterozygotes for pathogenic *LPL* variants, some of whom were evaluated for decades. Baseline untreated TG levels ranged from normal to severely elevated, and over time they fluctuated between the normal and mild-to-moderate HTG ranges, and mild-to-moderate and severe HTG ranges. About two-thirds of all TG measurements taken from all 15 patients were in the mild-to-moderate HTG range, and the remaining one-third were about equally divided between the normal and severe HTG ranges. Heterozygous LPL deficiency is not analogous to heterozygous FH, in which low-density lipoprotein (LDL) cholesterol levels do not fluctuate so widely within and between patients.

Heterozygosity for pathogenic variants in *LPL* is relatively common in the general population compared to homozygosity: up to 3% in our studies.[4,8,9] In contrast, biallelic rare *LPL* variants in FCS are associated with fully expressed severe HTG, but fortunately this is an ultrarare condition.[4] Heterozygotes are thus many times more prevalent in the population, but there is less familiarity with their phenotype. Others have reported variability of the TG phenotype previously.[15–19] For instance, in the pre-genomic era, John Brunzell and colleagues imputed heterozygote status in the parents of children with complete biochemical LPL deficiency.[15] They observed that one-quarter of parents had normal fasting TG levels, one half had mild-to-moderate HTG, and the remainder had severe HTG.[15] Although the DNA basis for the pathogenic *LPL* variants was not determined, the authors nonetheless commented on the wide variability of TG phenotypes in obligate heterozygotes for LPL deficiency.[15]

In the early genomic era, Wilson and colleagues studied large multigenerational Utah kindreds extended from the first index case of FCS with two copies of the *LPL* variant p.Gly215Glu, (also known as p.Gly188Glu, depending on the numbering of the propeptide sequence).[16,17] *LPL* p.Gly215Glu is recognized as the archetypal non-functional *LPL* missense variant, with a complete lack of lipolytic activity in vitro.[16] *LPL* p.Gly215Glu is also the most common pathogenic variant seen in cohorts of FCS patients.[6] Among

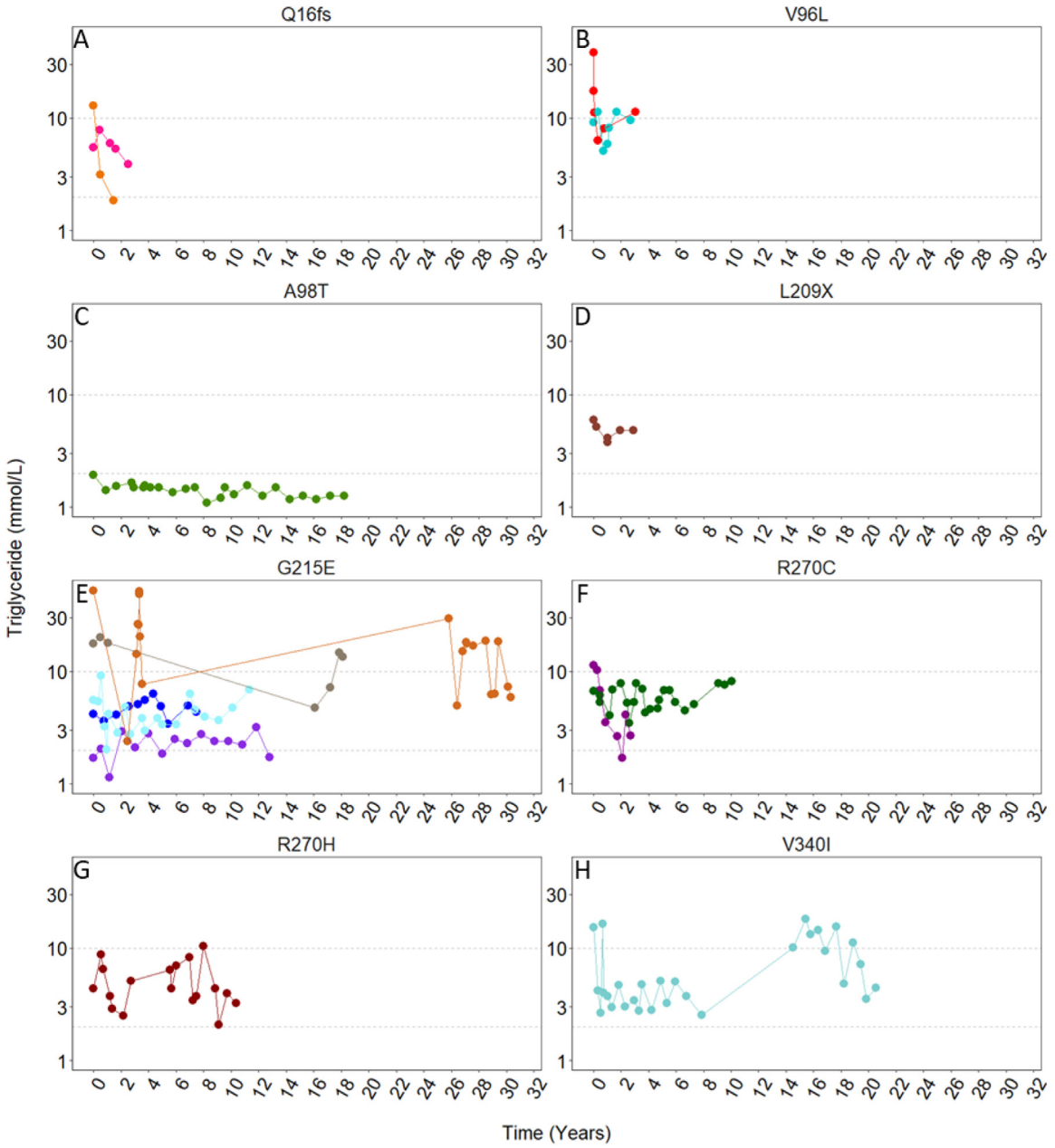

Fig. 2 Triglyceride trajectories of individuals heterozygous for pathogenic *LPL* variants. Longitudinal TG data for all patients (N = 15) plotted as days elapsed from first measurement (X-axis). Y-axis displays fasting plasma triglyceride level (mmol/L) using a $\log_{10}$ scale. Trajectories for patients heterozygous for A) p.Q16fs (p.Gln16fs), B) p.V96L (p.Val96Leu), C p.A98T (p.Ala98Thr), D) p.L209X (p.Leu209Ter), E) p.G215E (P.Gly215Glu), F) p.R270C (P.Arg270Cys), G) p.R270H (p.Arg270His), and H) p.V340I (p.Val340Ile). Horizontal lines at 2 and 10 mmol/L delineate the cut-offs for TG severity classifications (mild-to-moderate HTG is defined as TG between 2 and 9.9 mmol/L while severe HTG is TG > 10 mmol/L).

genotyped heterozygotes, Wilson and colleagues noted a wide range of possible fasting TG levels.[17] Data from our five heterozygotes for *LPL* p.Gly215Glu, similarly showed marked between-patient variability in TG levels (Figs. 1 and 2E).

What factors might explain the variability in TG phenotype in heterozygotes? We observed no clear relationship with degree of TG perturbation depending on the variant subtype, e.g. missense versus nonsense. It is possible that residual LPL activity in heterozygotes could contribute to a variable TG phenotype, although earlier studies showed that post heparin LPL activity in heterozygotes was highly variable – even above the normal range in some cases - and not clearly correlated with the TG level.[15] Furthermore, background polygenic (accumulation of specific small effect variants across the genome is known to elevate TG levels[8]) predisposition to HTG only weakly correlated (R^2=0.123) with the severity of the TG phenotype in the heterozygotes (data not shown), though a thorough analysis to determine if polygenic risk interacts synergistically with heterozygous

pathogenic LPL variant carrier status could not be performed due to lack of data from normolipidemic patients. But the earlier studies of Wilson and colleagues may provide some clues. Among Utah heterozygotes for *LPL* p.Gly215Glu, variability in TG levels was related to age: specifically 94% of heterozygotes < 40 years old had normal TG levels while two-thirds of those > 40 years old had HTG, of whom 15% had severe HTG.[17] The average age at referral in our cohort was 48.1 years, which is consistent with age-related predisposition to at least mild-to-moderate HTG and sometimes severe HTG. We did not observe clear temporal or age-related trends to increased TG levels. Also, our three female patients were not obviously different from males with respect to baseline TG and variability.

Other studies of kindreds with heterozygous *LPL* pathogenic variants reported that obesity, insulin resistance and type 2 diabetes worsened the severity of the HTG phenotype.[18–20] Unfortunately, our sample is too small – e.g. only four patients had diabetes - to evaluate the relationship of obesity and/or diabetes on HTG severity. However, our patients were all following medical advice, including stable adherence to medications.

With growing availability of genetic testing, heterozygosity for pathogenic *LPL* variants is increasingly being reported in genetic test results for patients with severe HTG. Our understanding of the clinical consequences of heterozygous LPL deficiency indicates that this genotype cannot be the direct cause of HTG. This is because up to 3% of people with normal lipids also have a heterozygous pathogenic *LPL* variant.[6,8,9] Furthermore, only 10% of patients with mild-to-moderate HTG[9] and only 15–20% of patients with severe HTG[8] are heterozygotes for pathogenic variants. Heterozygosity is a risk factor that raises the odds of expressing HTG, but is not causal. Furthermore, most heterozygotes with pathogenic *LPL* variants have normal lipids: 3% of the general population, who are never referred to clinic and will never undergo sequencing for HTG genes. The absolute number of normolipidemic heterozygotes dwarfs the 15-20% of heterozygotes seen among the 1 in 400 individuals referred with severe HTG. Because genetic testing for *LPL* is not pursued clinically for healthy people, the predominant relationship of this genotype with a normal lipid profile will not be appreciated by clinicians.

Genetic testing in adult patients is pursued in the context of severe HTG, which is operationally equivalent to multifactorial chylomicronemia syndrome (MCS).[21] In our experience some clinicians who order genetic testing in patients with severe and refractory HTG are expecting to find recessive biallelic pathogenic variants in *LPL, APOC2, APOA5, GPIHBP1* or *LMF1*, consistent with FCS. However, this genotype is present in only 1-5% of adults with severe HTG.[4,6,8,22–24] Instead, 15–20% of severe HTG patients are heterozygous for a single copy of such a variant in one of these five genes.[4,8,24] Thus, heterozygosity is consistent with predisposition to MCS or severe HTG, but it cannot be considered causal.[4,8,9] A single copy of a pathogenic variant in an FCS gene like *LPL* merely raises the risk for developing MCS/severe HTG.

In our experience, some clinicians when seeing the report of a heterozygous pathogenic *LPL* variant in a patient with severe HTG assume that this indicates "autosomal dominant HTG". But such a condition does not exist. Evidence against existence of autosomal dominant HTG is: (1) absence of vertical transmission, i.e. no co-segregation of heterozygous *LPL* pathogenic variants and HTG in multigenerational families;[16–20] (2) the large absolute number of normolipidemic individuals with heterozygous pathogenic variants;[6,8,9] (3) wide variability of the TG phenotype in heterozygotes over time; and (4) the dependence of expression of the phenotype on non-genetic factors such as increased age, obesity and diabetes.[17–20]

Finally, compared to other variables in the standard lipid profile, TG routinely shows much wider variability over time.[25] The intrinsic dynamic variability of TG could also have contributed to the observed fluctuations in our heterozygotes. In addition, colleagues from Denmark used a different design but similarly found that genetic determinants of baseline mild-to-moderate HTG predicted future pancreatitis, an endpoint that is associated typically with severe HTG;[26] this again suggests potential wide variability of TG levels over time.

Thus, genetic susceptibility to severe HTG or MCS in adults follows probabilistic and not deterministic principles.[6] 15–20% of those with severe HTG are susceptible because of heterozygosity for a pathogenic variant in a FCS gene. Another 35–50% have a high polygenic SNP score for TG, compared to only 10% of the general population.[4,8,27] Genetically susceptible adults can also have secondary non-genetic exacerbating factors such as older age, obesity, diabetes, insulin resistance, alcohol use, poor diet, etc. Finally, the degree of TG elevation in MCS/severe HTG can sometimes be just as severe as in FCS.[21] Operationally and clinically, these both warrant similar acute management and assertive novel treatments for long term control.[27] But in absolute terms, complex MCS/severe HTG is at least 100-times more prevalent than true recessive FCS, of which 80% is LPL deficiency.[4]

Thus, the TG phenotype of individuals heterozygous for *LPL* pathogenic variants is highly variable both within and between patients. *LPL* heterozygotes have TG phenotypes ranging from normal to severe HTG, even over relatively short periods of time. The analogy with heterozygous FH is inappropriate given the marked variability in the phenotype. HTG is a less stable phenotype than hypercholesterolemia, with more types of genetic determinants, including polygenic determinants, and secondary non-genetic factors playing a large role in phenotypic expression. Additionally, TG measurements at a single time point in a heterozygote may not sufficiently describe the TG phenotype. Finally, it would be of interest to determine whether heterozygotes for pathogenic variants in the other four FCS genes show similar phenotypic variability.

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Declarations of Competing Interest

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CRediT authorship contribution statement

Shehan D. Perera: Visualization, Formal analysis, Methodology, Writing – original draft. **Jian Wang:** Data curation, Formal analysis, Writing – review & editing. **Adam D. McIntyre:** Data curation, Formal analysis, Writing – review & editing. **Jacqueline S. Dron:** Data curation, Formal analysis, Writing – review & editing. **Robert A. Hegele:** Visualization, Formal analysis, Methodology, Writing – original draft, Data curation, Writing – review & editing.

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Supplementary materials

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