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Review

Allelic and phenotypic spectrum of plasma triglycerides ☆

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ABSTRACT

The genetic underpinnings of both normal and pathological variation in plasma triglyceride (TG) concentration are relatively well understood compared to many other complex metabolic traits. For instance, genome-wide association studies (GWAS) have revealed 32 common variants that are associated with plasma TG concentrations in healthy epidemiologic populations. Furthermore, GWAS in clinically ascertained hypertriglyceridemia (HTG) patients have shown that almost all of the same TG-raising alleles from epidemiologic samples are also associated with HTG disease status, and that greater accumulation of these alleles reflects the severity of the HTG phenotype. Finally, comprehensive resequencing studies show a burden of rare variants in some of these same genes – namely in *LPL*, *GCKR*, *APOB* and *APOA5* – in HTG patients compared to normolipidemic controls. A more complete understanding of the genes and genetic variants associated with plasma TG concentration will enrich our understanding of the molecular pathways that modulate plasma TG metabolism, which may translate into clinical benefit. This article is part of a Special Issue entitled Triglyceride Metabolism and Disease.

1. Introduction

Plasma total triglyceride (TG) concentration integrates the TG content of heterogeneous lipoprotein species, including intestinally-derived chylomicrons, hepatically-derived very low-density lipoprotein (VLDL) and their remnants together with the small amount of TG in low-density lipoprotein (LDL) and high-density lipoprotein (HDL) particles. While the totality of evidence suggests that elevated plasma TG, particularly in the post-prandial state, increases the risk of CVD independent of other factors [1–7], the case has not been straightforward to make. Elevated TG typically co-exists with a range of clinical and biochemical comorbidities that also increase cardiovascular disease (CVD) risk, such as obesity, metabolic syndrome, and type 2 diabetes [8], which obscures a clear relationship with CVD outcomes. Recent technological advances have permitted more intensive study of the genetic determinants of plasma TG; perhaps a more complete understanding of these determinants – and the biological pathways to which they point – could help further clarify our understanding of the TG-CVD link and might also suggest new targets for treatment of patients with particularly recalcitrant presentations of hypertriglyceridemia (HTG) and perhaps ultimately reduce clinical CVD endpoints.

As an archetypal complex quantitative trait, plasma TG has both genetic and environmental determinants. Genome-wide association studies (GWAS) and high-throughput resequencing of genomic DNA have identified many common and rare variants that are strongly associated with plasma TG. Furthermore, genetic determinants of population-based plasma TG levels within a narrow "normal" range are also determinants of extreme phenotypes, such as severe HTG. Here, we review recent progress in our understanding of the genetic determinants of plasma TG, including key genes and variants found through genome-wide association studies (GWAS), resequencing studies and complementary experimental approaches. We will describe how genes and variants collectively influence plasma TG concentration both in the healthy general population and in patients with extreme biochemical phenotypes. This understanding could provide the foundation for experiments to study new mechanisms and targets, possibly leading to new thinking about ontology, diagnosis, prognosis and therapy of HTG.

Abbreviations: ABL, abetalipoproteinemia; ANGPTL3, angiopoietin-like 3; ANGPTL4, angiopoietin-like 4; APOA4, apolipoprotein A-IV; APOA5, apolipoprotein A-V; APOB, apolipoprotein B; APOC2, apolipoprotein C-II; APOC3, apolipoprotein C-III; APOE, apolipoprotein E; CAD, coronary artery disease; cld, combined lipase deficiency; CREB3L3, cAMP responsive element binding protein 3-like 3; CVD, cardiovascular disease; eQTLs, expression quantitative trait loci; ER, endoplasmic reticulum; FCH, familial combined hypolipidemia; FGF21, fibroblast growth factor 21; GALNT2, UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 2; GK, glucokinase; GKRP, glucokinase regulatory protein; GLGC, Global Lipids Genetics Consortium; GPIHBP1, glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1; GWAS, genome-wide association studies; HDL, high-density lipoprotein; HHBL, homozygous hypobetalipoproteinemia; HNF4α, hepatocyte nuclear factor 4 alpha; HTG, hypertriglyceridemia; IRS1, insulin receptor substrate 1; LDL, low-density lipoprotein; LMF1, lipase maturation factor 1; LOF, loss-of-function; LPL, lipoprotein lipase; MLXIPL, Max-like protein X interacting protein-like; MTP, microsomal triglyceride transfer protein; PEPCK, phosphoenolpyruvate carboxykinase; PINX1, PIN2/TERF1 interacting, telomerase inhibitor 1; PLA2G6, phospholipase A2 group VI; PPARα, peroxisome proliferator-activated repressor alpha; TG, triglyceride; TRIB1, tribbles homolog 1; VLDL, very low-density lipoprotein

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2. Genetic determinants of "normal" plasma TG concentrations

2.1. GWAS-identified TG-associated genes

2.1.1. General findings from the Global Lipids Genetics Consortium

Since late 2007, GWAS have contributed significantly to the identification of genetic loci associated with a multitude of complex human traits, including plasma lipid concentrations. The general background and experimental design parameters for GWAS are reviewed elsewhere [9–11]. By now there is no question that these studies have yielded more new and potentially valuable biological leads in the last 4 years than all earlier genetic experiments provided over the preceding 30 years. For instance, in 2010 the Global Lipids Genetics Consortium (GLGC) published a landmark GWAS meta-analysis carried out in >100,000 subjects that identified 95 loci associated with plasma lipid concentrations [12], including 32 loci associated with plasma TG (Table 1). Interestingly, most TG-associated loci were also modestly associated with either HDL or LDL cholesterol levels, suggesting extensive pleiotropic effects among genes modulating lipid and lipoprotein metabolism [13]. Many of these loci were further replicated in multi-ethnic cohorts, in patients with extreme lipid and lipoprotein phenotypes, and were also associated with increased coronary artery disease (CAD) risk.

The effect sizes of common TG-associated variants were found to vary widely across the associated loci (Table 1). For example, common variants at *APOA5* have the largest effect, increasing plasma TG by ~0.2 mmol/L (~17.0 mg/dL) per risk allele, whereas smaller effect variants such as in the *PLA2G6* locus only increase plasma TG by ~0.02 mmol/L (~1.54 mg/dL). The vast majority of TG-associated variants have effect sizes 1/5 to 1/10 of *APOA5* variants, and cumulatively these 32 GWAS-identified TG-associated variants explain ~25–30% of the genetic contribution to plasma TG, which corresponds to ~10% of total variability of the trait. It is considered likely that additional undiscovered loci will have even smaller effects, since they have so far eluded detection by GWAS even in massive epidemiologically-sized samples. Also, rare variants with either small or large effects are intentionally not represented on the predominant microarray platforms used to genotype GWAS samples and these could represent an additional genetic source of variation. Thus, new experimental approaches to complement current common polymorphism-based GWAS are required to find additional loci and variants.

Complementary analyses support a mechanistic role in lipoprotein metabolism for at least some GWAS-identified loci. First, many lipid-associated GWAS loci including ~1/3 of TG-associated loci were subsequently identified as being expression quantitative trait loci (eQTLs), meaning that the same common variants associated with plasma TG levels were also associated with transcript concentrations of ≥1 gene in liver, omental or subcutaneous fat [12]. This is strongly suggestive evidence for involvement of genes via regulatory or promoter elements in the modulation of plasma TG concentration. Second, in vivo overexpression and knockdown studies for the novel HDL/TG-associated GWAS gene *GALNT2* showed mechanistic evidence for an inverse relationship between *Galnt2* expression and lipoprotein concentrations [12]. If even a few TG-associated GWAS loci from such preliminary experiments pan out, they will greatly expand the range of putative genes and gene products that modulate plasma TG concentration.

2.1.2. TG-associated loci and CVD risk

The GLGC further showed that several TG-associated GWAS loci are also associated with increased CAD risk. In particular, 6 TG-associated

Table 1
Loci identified by the GLGC meta-analysis associated with plasma TG concentration, HTG and CAD risk.

Locus	CHR	SNP	Plasma TG concentration [12]			HTG [59]		Effect on CAD risk [12]	
			Risk allele	Effect size mmol/L (mg/dL)	P-value	Odds ratio	P-value	Increases risk?	P-value
APOA5	11	rs964184	G	0.19 (16.95)	7.0×10^{-240}	3.43	1.12×10^{-25}	+	2×10^{-8}
GCKR	2	rs1260326	T	0.10 (8.76)	6.0×10^{-133}	1.64	1.97×10^{-7}	+	0.14
LPL	8	rs12678919	A	0.15 (13.64)	2.0×10^{-115}	2.21	3.5×10^{-5}	+	7×10^{-4}
MLXIPL	7	rs7811265	A	0.09 (7.91)	9.0×10^{-59}	1.63	3.3×10^{-4}	−	0.06
TRIB1	8	rs2954029	A	0.06 (5.64)	3.0×10^{-55}	1.50	3.8×10^{-5}	+	5×10^{-5}
APOB	2	rs1042034	T	0.07 (5.99)	1.0×10^{-45}	1.28	0.032	+	0.08
ANGPTL3	1	rs2131925	T	0.06 (4.94)	9.0×10^{-43}	1.51	1.0×10^{-4}	−	0.14
*APOE**	19	rs439401	C	0.06 (5.50)	1.0×10^{-30}	0.95	0.68	+	7×10^{-5}
CILP2	19	rs10401969	T	0.09 (7.83)	2.0×10^{-29}	1.72	6.8×10^{-3}	+	5×10^{-4}
FADS1-2–3	11	rs174546	T	0.04 (3.82)	5.0×10^{-24}	1.20	0.054	−	0.54
PLTP	20	rs4810479	T	0.04 (3.32)	5.0×10^{-18}	1.06	0.60	−	0.16
HLA	6	rs2247056	C	0.03 (2.99)	2.0×10^{-15}	1.21	0.076	+	0.11
NAT2	8	rs1495743	G	0.03 (2.97)	4.0×10^{-14}	1.07	0.52	+	2×10^{-5}
GALNT2	1	rs1321257	G	0.03 (2.76)	2.0×10^{-14}	1.16	0.12	+	0.06
LIPC	15	rs261342	G	0.03 (2.99)	2.0×10^{-13}	0.84	0.13	−	0.46
CETP	16	rs7205804	G	0.03 (2.88)	1.0×10^{-12}	1.20	0.056	+	0.05
JMJD1C	10	rs10761731	A	0.03 (2.38)	3.0×10^{-12}	1.00	1.00	−	0.17
TIMD4	5	rs1553318	C	0.03 (2.63)	4.0×10^{-12}	1.21	0.054	+	0.58
KLHL8	4	rs442177	T	0.03 (2.25)	9.0×10^{-12}	1.36	1.5×10^{-3}	+	0.06
FRMD5	15	rs2929282	T	0.06 (5.13)	2.0×10^{-11}	1.06	0.79	+	0.01
MAP3K1	5	rs9686661	T	0.03 (2.57)	1.0×10^{-10}	1.19	0.12	+	0.003
COBLL1	2	rs10195252	T	0.02 (2.01)	2.0×10^{-10}	1.13	0.19	+	0.34
LRP1	12	rs11613352	C	0.03 (2.70)	4.0×10^{-10}	1.11	0.35	−	0.91
TYW1B	7	rs13238203	C	0.09 (7.91)	1.0×10^{-9}	1.30	0.47	−	0.22
PINX1	8	rs11776767	C	0.02 (2.01)	1.0×10^{-8}	1.00	1.00	−	0.02
ZNF664	12	rs12310367	A	0.03 (2.42)	1.0×10^{-8}	0.97	0.77	+	0.004
CAPN3	15	rs2412710	A	0.08 (7.00)	2.0×10^{-8}	1.50	0.14	+	0.04
CYP26A1	10	rs2068888	G	0.03 (2.28)	2.0×10^{-8}	1.29	5.9×10^{-3}	+	0.001
IRS1	2	rs2943645	T	0.02 (1.89)	2.0×10^{-8}	1.20	0.061	+	4×10^{-4}
CTF1	16	rs11649653	C	0.02 (2.13)	3.0×10^{-8}	1.05	0.59	+	0.49
MSL2L1	3	rs645040	T	0.03 (2.22)	3.0×10^{-8}	1.06	0.58	+	0.15
PLA2G6	22	rs5756931	T	0.02 (1.54)	4.0×10^{-8}	1.04	0.70	−	0.08

CAD, coronary artery disease; CHR, chromosome; GWAS, genome-wide association study; HTG, hypertriglyceridemia; SNP, single nucleotide polymorphism; TG, triglyceride. *The TG-associated *APOE* variant is not associated with CAD; P-value is shown for the LDL/HDL-associated variant from the *APOE* locus.