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CARDIOVASCULAR GENETICS (B MITCHELL, SECTION EDITOR)

Genetic and Epigenetic Regulations of Post-prandial Lipemia

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Abstract

Purpose of Review Post-prandial lipemia (PPL), characterized by elevated levels of triglyceride (TG) following a meal, is an independent risk factor for cardiovascular disease. This review summarizes current knowledge on the genetic and epigenetic determinants of the PPL TG response and provides perspectives on future directions.

Recent Findings Recent studies suggested that PPL-related traits have heritability between 38 and 80%. Genomics studies identified genetic variants in or near *APOA1/C3/A4/A5* cluster region affecting PPL TG levels. Epigenomics studies found DNA methylation levels of many genes known to be related to lipid metabolism including *CPT1A* gene are associated with fasting TG and PPL TG.

Summary Both genetic polymorphisms and epigenetic modifications are important determinants of PPL variation. Epigenetics may have even more significant impact than genetic variants on PPL. Further studies with multi-omics system biology approach are needed to fully elucidate the mechanisms of PPL regulation to combat the atherogenic effect of PPL.

Keywords Post-prandial lipemia · Triglyceride · GWAS · EWAS · Genetics · Epigenetics

Introduction

Cardiovascular disease (CVD) is the leading cause of death in the USA with prevention and treatment efforts largely targeted at traditional CVD factors (e.g., fasting LDL, blood pressure, adiposity, and smoking). Identifying novel CVD risk factors and understanding more completely the mechanisms by which the established risk factors exert their effects remain a priority of CVD risk prevention, so that these risks can be more fully mitigated.

The association of hypertriglyceridemia (HTG) with CHD has long been recognized. HTG has been consistently shown through longitudinal [1–3] to increase CVD risk independently of other known risk factors, and genetic variants that are associated specifically with elevated triglycerides are also associated with CVD [4–6]. The importance of HTG (triglyceride (TG) > 150 mg/dL) as a CVD risk factor is highlighted by its high prevalence (i.e., frequency of 25% in the USA [7]). While elevated levels of fasting TG have long been known to predict CVD, fasting levels do not reflect the wide fluctuations and sustained high levels that can occur throughout the day. Unlike the relatively constant plasma LDL-C level, circulating TG increases after a meal, peaking at ~4 h and slowly returning to the fasting level after 6–8 h following a meal [8–12]. Consequently, the significance of TG as a CVD risk factor should be recognized in the context that most of the day is spent in the post-prandial state (i.e., post-prandial lipemia, PPL).

A systematic assessment of PPL requires an oral fat tolerance test (OFTT) whereby the fasting subject ingests a standardized fat meal and TG levels are measured at regular intervals for up to 6 h to determine the rate of TG increase and clearance. Multiple cross-sectional studies have now been revealed an association between an elevated TG response after a standardized OFTT and delayed clearance of TGs with presence of CVD [13–17]. Moreover, non-fasting TG levels have been significantly associated with incident CVD events, and this association is stronger than that for fasting TG and is independent of LDL and other known CVD risk factors [18–21].

The atherogenic mechanisms underlying PPL are only broadly understood. Initially, there is a rapid and prolonged change in circulating lipid profiles after ingesting a high-fat meal, characterized by production of TG-rich remnant

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particles from lipolysis of chylomicrons and generation of very low density lipoproteins from liver, as well as a reduction in high density lipoprotein (HDL) [22–25]. These changes are pro-atherogenic and occur in the context of post-prandial inflammation with ensuing endothelial dysfunction [26] and pro-thrombotic activity [24]. Post-prandial inflammation appears to be the central event triggering these atherogenic changes that follow prolonged/intensified PPL [27, 28]. Consistent with the post-prandial inflammation state, a single high-fat meal induces increased secretion of the inflammatory biomarker interleukin-6 (IL-6) during the post-meal period and activation of white blood cells in terms of both the cell count and individual cell activation markers (e.g., granulocyte and mononuclear cells) [29, 30•]. Exactly how this sequence of events unfolds is unclear.

Behavioral and Clinical Determinants of PPL

Variability in the PPL response at the population level is influenced by a range of factors, including sex, age, baseline TG level, aerobic capacity, adiposity, diet, and disease status (e.g., diabetes, insulin resistance, periphery artery disease, hypertension, coronary artery diseases, and inflammation) [2, 8, 13–17, 31]. As an example, there has been much interest in studying the effect of exercise on PPL [32], with numerous studies showing that acute exercise prior to a high-fat meal can effectively attenuate the PPL response (e.g., see review by Teeman et al. [33]). Much current research has been directed into characterizing the optimal duration, intensity, and types of physical exercise that most efficiently reduce the PPL response.

Genetic Determinants of PPL

The genetic basis of HTG has been well recognized from early studies of monogenetic forms of this disorder. The most common monogenetic forms of HTG are due to loss-of-function mutations in genes related to metabolism of triglyceride-rich lipoproteins, such as *LPL*, *APOC2*, *APOA5*, *LMF1*, *GPIHBP1*, and *GPD1* [34]. Of these, a loss of function mutation in the lipoprotein lipase gene (*LPL*) is the most common etiology of monogenic HTG. The main function of *LPL* is to hydrolyze TG in chylomicrons and VLDL particles. In contrast to these monogenic forms, the majority of HTG is due to a polygenic form of the condition. Heritability analyses have revealed that genetic effects can account for 54–59% of the variation of fasting TG in population [35, 36]. In fact, the most recent large-scale genome-wide association studies (GWAS) have identified at least 224 common and low-frequency SNPs from 137 genes/regions that are associated with triglyceride levels, mostly measured in the fasting state [37]. Among these genomic loci are many with known functions in lipid metabolism, such as *LPL*, *APOA5*, *APOB*, *APOC1*, *APOE*, and *GCKR*. However, it is currently unknown how most of other associated loci outside of these known lipid metabolism genes are involved in the regulation of TG metabolism.

The heritability of the PPL TG, assessed as the integrated area under the curve of TG across 6 h, was estimated at 38% in Amish subjects from the Heredity and Phenotype Intervention (HAPI) Heart Study [38]; the slope of the TG increase at 3.5 h after OFTT had a heritability of ~ 80% in the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) study [39•]. Multiple genetic association studies of PPL TG have been carried out, most utilizing the candidate gene approach and focusing on genes known to be related to lipid absorption, apolipoproteins, and lipid clearance pathways, including the *APOA1/C3/A4/A5* gene cluster, *ABCA1*, *CETP*, *GCKR*, *IL6*, *LPL*, *PLIN1*, and*TCF7L2* [40, 41]. Unlike candidate gene studies, the GWAS approach has the appeal of offering an agnostic survey of the whole genome and could discover novel candidates.

To date, GWAS of PPL TG have been conducted in only the Amish HAPI Heart [11] and GOLDN studies [42••]. In 2008, the Amish HAPI Heart Study identified a null mutation (R19X) in *APOC3* that is carried by ~ 5% of Amish subjects in Lancaster County, PA, USA. The R19X carriers had approximately one half of the levels of apoC-III protein compared to non-carriers and demonstrated a significantly reduced PPL TG excursion during the OFTT. These subjects also had a relatively cardioprotective risk profile that included lower coronary calcification scores [11]. This cardioprotective phenotype occurs because apoC-III inhibits lipoprotein lipase (LPL), the primary hydrolyzer of TG-rich chylomicrons. The mutation leads to increased LPL activity, thereby promoting chylomicron hydrolysis and reducing PPL.

The GWAS of PPL conducted in the GOLDN Study, which was based on 872 subjects of European ancestry, identified two SNPs significantly associated with PPL TG excursion at genome-wide thresholds of significance level (i.e., $p < 5E-08$), one of which, rs964184, was replicated in the Amish HAPI Study [42••]. rs964184 is located near *ZPR1* and close to the *APOA1/C3/A4/A5* cluster. rs964184 falls in a linkage disequilibrium block that includes *APOA5*, the gene-encoding apolipoprotein A5, a component of HDL and which plays a major role in regulating important determinant of plasma TG level. rs964184 has been previously associated with fasting TG [43], TG response to fenofibrate [44], fat intake and TG response interaction [45], metabolic syndrome [46], and coronary artery disease [47].

Epigenetic Determinants of PPL

The two SNPs significantly associated with PPL TG in the GOLDN Study (rs964184 and rs10243693) account for

only 4.5% of the variation in PPL TG AUC in the GOLDN population [42••, 48•], and the Amish *APOC3* R19X variant (rs76353203) accounts for virtually none of the phenotypic variation in European populations because the frequency of this variant is so rare outside of the Amish. Even for the relatively well-studied fasting TG measure, it is estimated that one half of the variance in this trait cannot be explained by the *common* and *rare* variants identified in current GWAS [49]. For example, 86 *common* SNPs associated with increased TG through meta-analysis account for less than 12% variance of triglyceride levels in the Framingham heart study [43, 50]. The missing heritability of HTG could be due to unstudied rare genetic variants, gene-gene interactions, epigenetics, and/or gene-environment interactions [49].

Epigenetic changes constitute a potential source of variability in PPL TG excursions that is not captured by genome-wide genotype data. Epigenetic changes refer to molecular factors or processes that do not affect the DNA sequence but can influence gene expression [51] via several mechanisms, including the following: (1) methylation of DNA nucleotide base almost exclusively at cytosines of CpG (5'—C—phosphate—G—3') dinucleotides in human; (2) biochemical modification of the histone molecules that package DNA sequences; and (3) non-coding RNAs that interact with DNA methylation and chromatin modification machinery. Epigenetics has been shown to regulate many important biological processes, including development, diseases, and response to behaviors [52–56]. Epigenetic regulation can be modified by both genetic and environmental factors, for example, genetic polymorphisms can act as quantitative trait loci (QTL) to influence epigenetic modification of DNA sequence; in addition, epigenetic modification of DNA sequence can be dynamic and respond to environmental changes. Thus, epigenetic variation represents the interface of gene and environment interaction, and this provides another source of variation in PPL response across subjects. This review will focus on DNA methylation, the most studied mechanism of epigenetic regulation.

Similar to GWAS, an epigenome-wide association study (EWAS) examines associations between epigenetic variation, mostly DNA methylation variation, and a particular trait. To date, six EWAS have been published of fasting TG (see Table 1). These have revealed associations of fasting TG with DNA methylation sites at 34 unique loci mapping to 17 different genes [48•, 59•, 60•, 61•, 62•, 63•]. The only EWAS of PPL TG published to date is from the GOLDN Study [57••]. This analysis was based on 979 GOLDN subjects who underwent a standard OFTT, and DNA was purified peripheral lymphocytes at baseline before OFTT. The goal of this analysis was to identify DNA methylation sites at baseline that predicted PPL TG response to the OFTT. Eight loci at five genes (*LPP*, *CPT1A*, *APOA5*, *SREBF1*, and *ABCG1)* had methylation levels at baseline that were significantly associated with PPL TG at genome-wide significance ($P < 1.1 \times 10^{-7}$) [57••]; interestingly, these eight CpG sites together account for 14.9% of the variance in PPL TG and 16.3% of the phenotypic variance in fasting TG in the GOLDN Study cohort [57••]; in contrast, the two previously identified genetic loci for PPL TG (rs964184 and rs10243693) explained only 4.5% phenotypic variance for both PPL TG AUC and fasting TG. This suggests that epigenetics may be a more significant contributor than DNA sequence variation to PPL TG variability at the population level. Four out of the five identified genes have established roles in lipid metabolism; four CpG loci themselves, mapping to the genes *CPT1A*, *APOA5*, *SREBF1*, and *ABCG1*, have been directly reported to be associated with fasting TG in European populations (KORA and InCHIANTI) [63•]. The association of PPL TG with *CPT1A* methylation, which was the most strongly associated locus, was particularly noteworthy because of the function of this gene. *CPT1A* (Carnitine Palmitoyltransferase 1A) is a key enzyme for the mitochondrial oxidation of long-chain fatty acid, catalyzing the transfer of the acyl group of long-chain fatty acid-CoA conjugates onto carnitine that is essential for the mitochondrial uptake of long-chain fatty acids, which is a metabolism product and component of triglyceride, and their subsequent beta-oxidation. Thus, it is not surprising that *CPT1A* might play major role in PPL and fasting triglyceride metabolism.

It must be pointed out that the baseline epigenetic profiles correlated with PPL TG response could be inherited intergenerationally or could be the consequence of certain behavior/environmental factors. Besides the heritable epigenetic profiles in epigenome, the aforementioned behavioral/environmental factors that are associated with PPL TG response variation, such as exercise, diet, and smoking, could also modify epigenetic machinery and gene transcription both acutely and chronically, which in turn could alter the PPL TG response after meal intake. For example, both acute and chronic exercise could induce widespread DNA methylation and gene expression changes in skeletal muscle and in peripheral blood cells [64–66]. One time or long-term dietary interventions also could induce significant DNA methylation and gene expression changes [67, 68]. It was found that dietary polyunsaturated fatty acids can modify the epigenome and some of the methylation changes were correlated with changes in plasma triglyceride [68, 69]. The interplay among genetics, epigenetics, and environmental/behaviors factors and how these factors may collectively lead to an abnormal PPL TG response and increased CVD risk are depicted in a working hypothesis model in Fig. 1. As implied by this model, an integrative multi-omics, multi-system approach is necessary to dissect the pro-atherosclerosis mechanism of HTG.

Table 1 Epigenome-wide association studies of TG

References	Triglyceride measures	Discovery samples	Replication samples	Main tissues sources	Major findings on TG-associated CpG loci
Lai et al. 2016 [57••]	After standardized high-fat meal challenge	Two third ($n = 653$) of the 979 European from GOLDN study by random splitting	One third ($n = 326$) of the 979 European from GOLDN study	CD4+ T cells	4 CpG loci in 3 genes (*CPT1A*, *APOA5*, and *SREBF1*)
Truong et al. 2017 [58]	Fasting	5 French-Canadian families ascertained on venous thromboembolism ($n = 199$)	1592 unrelated patients with venous thromboembolism from the MARTHA study	Whole blood	2 CpG sites in gene *ABCG1* and *PHGDH*
Braun et al. 2017 [59•]	Fasting	725 subjects from RSIII-1 of the Rotterdam Study	767 subjects from RSII-3 and RSIII-2 of the Rotterdam Study	Whole blood	5 CpG sites in 4 genes (*DHCR24*, *CPT1A*, *ABCG1*, and *SREBF1*)
Hedman et al. 2017 [60•]	Fasting except for replication samples	2 cohorts: the FHS offspring cohort ($n = 1494$) and the PIVUS ($n \leq 812$)	3 cohorts: the LBC1921 ($n \leq 380$), LBC1936 ($n \leq 654$), the GOLDN ($n = 991$)	Whole blood	19 CpG sites in 10 genes (*SARS*, *PHGDH*, *TXNIP*, *SLC7A11*, *GARS*, *CPT1A*, *SREBF1*, *VPS25*, *SLC1A5*, *ABCG1*) and 1 region
Sayols-Baixeras et al. 2016 [61•]	Fasting	645 Europeans from the REGICOR study in Catalonia (Spain)	2542 subjects from the Framingham Offspring Study	Whole blood	10 CpG loci in 6 genes (*TXNIP*, *SLC7A11*, *MYLIP*, *CPT1A*, *SREBF1* and *ABCG1*)
Dekkers et al. 2016 [62•]	76% fasting and 24% non-fasting samples	3296 individuals from 6 Dutch cohorts in the Biobank-based Integrative Omics Study (BIOS) Consortium	None	Whole blood	Using Mendelian randomization analysis based on GWAS of TG, this study did not observe the effect of DNA methylation on TG level; rather, this study found TG induced differential methylation in 3 CpG loci, which are associated with differential expression of *CPT1A* and *SREBF1*
Pfeiffer et al. 2015 [63•]	Fasting	1776 subjects from the KORA F4 study in Southern Germany	Whole blood from 971 subjects in the KORA F3 ($n = 499$) and the InCHIANTI study ($n = 472$) in Southern Germany; Human adipose ($n = 634$) and skin ($n = 395$) samples of MuTHER study	Whole blood	8 CpG sites in 6 genes/regions (*ABCG1*, *TXNIP*, *SREBF1*, *CPT1A*, *MIR33B/SREBF1*, *APOA5*)

MuTHER study, the Multiple Tissue Human Expression Resource study; *BIOS Consortium*, Biobank-based Integrative Omics Study Consortium, including the Cohort on Diabetes and Atherosclerosis Maastricht (CODAM), LifeLines, Leiden Longevity Study, the Netherlands Twin Register (NTR), Rotterdam Study, and Prospective ALS Study Netherlands (PAN), REGICOR study (REgistre GIroni del COR) study; *FHS*, Framingham Heart Study; *GOLDN study*, Genetics of Lipid Lowering Drugs and Diet Network; *KORA F4 study*, Cooperative Health Research in the Region of Augsburg F4 cohort; *KORA F3 study*, Cooperative Health Research in the Region of Augsburg F3 study; *LBC1921*, Lothian Birth Cohorts of 1921; *LBC1936*, Lothian Birth Cohorts of 1936; *InCHIANTI study*, Invecchiare in Chianti, Aging in the Chianti Area study; *PIVUS study*, Prospective Investigation of the Vasculature in Uppsala Seniors Study; *MARTHA study*, the MARseille Thrombosis Association study

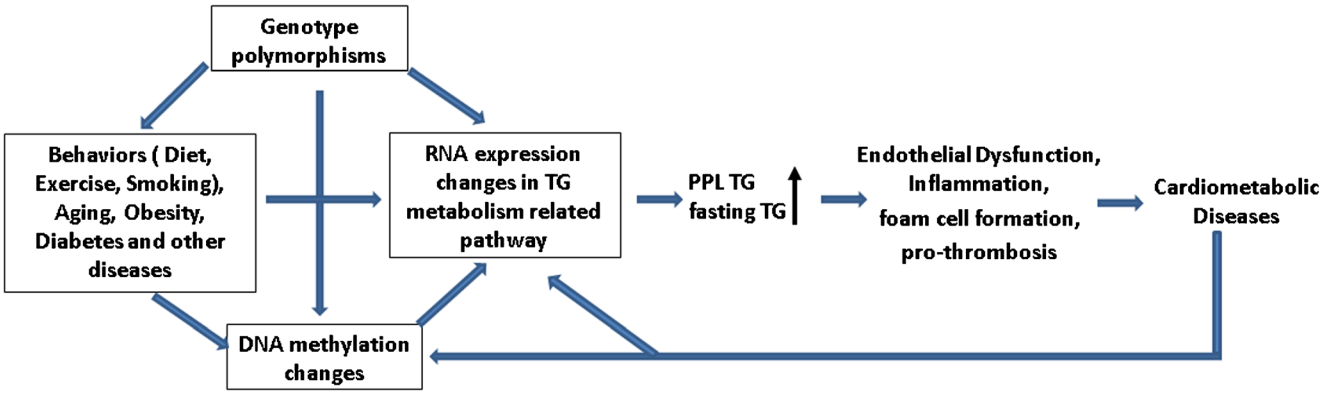

Fig. 1 Theoretical working model on genetic and epigenetic determinants of PPL TG

Conclusions and Future Directions

Genetic and epigenetic association studies are complementary strategies to identify molecular mechanisms underlying adverse PPL TG excursion after meals. However, we are still in the infancy stage with only a handful of genetic variants and DNA methylation loci identified that explain only a small portion of the population variation in PPL TG excursion. Further work is needed on several fronts to advance our understanding of PPL TG as a risk factor for cardiovascular diseases and its management. First, we must increase the sample size for genomic, epigenetic, and epidemiologic studies of PPL TG. Currently, PPL has been understudied in large population studies due to the resource demand in administering a standard fat meal challenge and time course blood sampling. There is also not a solid consensus on the standards for the fat meal challenge. Second, we will need to devote efforts to dissect the dynamic changes in epigenomics, transcriptomic, metabolomics, and proteomics along with PPL TG excursion. Multi-level-omics data has not yet been systematically collected over time for PPL TG. Although Mendelian randomization analysis has demonstrated a causal link between increased TG and cardiovascular risk, the mediating mechanisms remain largely unknown. Natural history studies with extended time course sampling of PPL TG excursions are needed to reveal such mediating signaling pathways and pathological events that are perturbed by the increased PPL TG and which eventually lead to foam cell formation and atherosclerosis plaque development. Third, we will need to design effective behavior intervention to effectively manage PPL TG and prevent CVD. To date, multiple behavioral factors such as diet, exercise, and smoking have been associated with PPL TG variation, but it is not clear what kinds of diet combination or what kind of exercise regime would be optimal to reduce PPL TG exposure. Last but not the least, we will need to design more effective pharmacological treatment for managing PPL TG. Fibrates are the most often used drugs that could specifically target TG and lower TG levels by ~ 36% [70]; however, the cardiovascular outcome of fibrate therapy varied across different studies so far [71]. Moreover, fibrates could result in adverse effects such as increases in creatinine levels, myopathy, and rhabdomyolysis. Mechanistic genetic and epigenetic study of factors that influence PPL TG response could help the discovery of novel therapy targets.

Compliance with Ethical Standards

Conflict of Interest Dr. Xu declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal studies performed by any of the authors.

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- • Of importance
- •• Of major importance

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