

VIEWPOINT

# The common biological basis for common complex diseases: evidence from lipoprotein lipase gene

Cui Xie<sup>1</sup>, Zeng Chan Wang<sup>1</sup>, Xiao Feng Liu<sup>2</sup> and Mao Sheng Yang<sup>\*1</sup>

The lipoprotein lipase (LPL) gene encodes a rate-limiting enzyme protein that has a key role in the hydrolysis of triglycerides. Hypertriglyceridemia, one widely prevalent syndrome of LPL deficiency and dysfunction, may be a risk factor in the development of dyslipidemia, type II diabetes (T2D), essential hypertension (EH), coronary heart disease (CHD) and Alzheimer's disease (AD). Findings from earlier studies indicate that *LPL* may have a role in the pathology of these diseases and therefore is a common or shared biological basis for these common complex diseases. To examine this hypothesis, we reviewed articles on the molecular structure, expression and function of the LPL gene, and its potential role in the etiology of diseases. Evidence from these studies indicate that *LPL* dysfunction is involved in dyslipidemia, T2D, EH, CHD and AD; and support the hypothesis that there is a common or shared biological basis for these common complex diseases.

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## INTRODUCTION

The lipoprotein lipase (LPL) gene is located on 8p22, spans ~30 kb and contains 10 exons and encodes a rate-limiting enzyme called lipoprotein lipase. LPL has a key role in the hydrolysis of triglycerides (TG). In 1960, LPL deficiency was discovered by Havel and Gordon,<sup>1</sup> and several mutations were identified upon cloning the gene in 1991 by Henderson *et al.*<sup>2</sup> Subsequently, more subtle mutations were detected in the LPL gene, and some mutants are reputed to influence LPL activity and has a role in the disease's etiology.<sup>2–3</sup> *LPL* is one member of the triglyceride (TG) lipase gene family, which includes pancreatic lipase (PL), hepatic lipase (HL) and newly discovered endothelium lipase (EL).<sup>4</sup> It is a rate-limiting enzyme in the hydrolysis of triglyceride-rich particles,<sup>5</sup> such as chylomicron and very-low-density lipid (VLDL), thereby providing non-ester acids and 2-

monoacylglycerol for tissue use.<sup>6</sup> Recently, in addition to hydrolysis, LPL has been reported to be involved in lipid intake and clearance.<sup>7–10</sup> Variations in LPL gene sequence, expression and regulation may influence its function and contribute to diseases. The changes in LPL activity in adipose and muscle tissues suggest that LPL is regulated in a tissue-specific manner.<sup>4,11,12</sup> Several allelic variants were reported to affect the expression and activity of *LPL*. In this paper, we review the literature relating to *LPL* focusing on five diseases, namely dyslipidemia, type II diabetes (T2D), essential hypertension (EH), coronary heart disease (CHD) and Alzheimer's disease (AD) to see whether there is any common etiological mechanism involving *LPL*.

## LPL and dyslipidemia

LPL is the key enzyme in the hydrolysis of triglycerides packaged in chylomicron and

VLDL, thereby providing non-estered fatty acids (NEFA) and 2-monoacylglycerols for many tissues.<sup>8,9</sup> In adipose, NEFA is re-esterified for storage in the form of triacylglycerol (TAG); but in muscles, oxidation of NEFA is the major source of energy.<sup>6</sup> According to these studies above, it might be reasonable to considering *LPL* as the preferred candidate gene for the dyslipidemia.

The relationship between *LPL* and dyslipidemia is very well established and independent of ethnic background.<sup>1–3,13</sup> Several clinical observations have suggested that the patients with LPL deficiency suffer severe hypertriglyceridemia.<sup>3,14</sup> The genetic variants of *LPL* may have a role in determining lipid levels. A study by Jemaa *et al.*<sup>15</sup> in French patients (614 patients with myocardial infarction and 733 controls;  $P < 0.01$ ) indicated that there is an association between *LPL* rs328 C→G (Ser447Stop) polymorphism and hypertriglyceridemia. Their result is supported by Groenemeijer *et al.*<sup>16</sup> study in Dutch patients (820 patients of coronary artery disease;  $P = 0.044$ ), and by King *et al.* (1998) finding<sup>17</sup> and Yamada *et al.*<sup>18</sup> report (in 5213 Japanese individuals;  $P = 0.0007$ ). The above results are also supported by evidence from the Chinese samples. A genetic screen of *LPL* gene of 53 hypertriglyceridemia patients in 26 T2D Chinese pedigrees identified that three novel mutations, Lys312InsC, Thr361LnsA and double mutations Lys312InsC+Asn291Ser, were clinically associated with hypertriglyceridemia, which was further confirmed by the mutagenesis with significantly reduced LPL activity ( $P < 0.01$ ) and expression studies.<sup>19</sup> Yang *et al.*<sup>20</sup> found that two SNPs *Hind*III (rs320) and *Hinf*I (rs328) at *LPL* were associated with cholesterol levels ( $P = 0.0178$  and  $P = 0.0088$ , respectively) in Chinese cohort.

This association is further validated by LPL target therapy studies. Ross *et al.*<sup>21</sup> observed that intramuscular administration of an adeno-associated virus serotype 1 (AAV1) vector encoding the human *LPL*<sup>S447X</sup> variant cDNA (AAV1-*LPL*<sup>S447X</sup>) could normalize the dyslipidemia in *LPL*<sup>-/-</sup> mice, and Kodera *et al.* reported that anti-LPL autoantibody could elevate serum triglyceride levels by inhibiting 47% activity of LPL ( $P < 0.0001$ ).<sup>22</sup>

## LPL and T2D

T2D is widely prevalent in the world's populations and it is predicted that the prevalence will increase to 5.4% by the year 2025.<sup>17</sup> Both hereditary and environmental factors contribute to individual susceptibility; however, dysfunction of *LPL* may explain, at least in part, the prevalence of T2D.

<sup>1</sup>Laboratory of Disorder Genes, School of Public Health, Chongqing University of Medical Sciences, Chongqing, People's Republic of China; <sup>2</sup>Chongqing Medical University Library, Chongqing, People's Republic of China

\*Correspondence: Professor MS Yang, Laboratory of Disorder Genes, Chongqing University of Medical Sciences, School of Public Health, PO Box 109, 1 Yi Xue Yuan Road, Chongqing, 400016, People's Republic of China. Tel: +00 86 23 6848 6014; Fax: +00 86 23 6848 5111; E-mail: yangmaosheng@hotmail.com  
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Hözl *et al.*<sup>23</sup> reported a study that enrolled 85 heterozygous carriers of a missed (Gly188-Glu) mutation or a splice site mutation (c-in position-3 at the acceptor splice site of intron 6) in the LPL gene and 108 non-carriers. Their results indicated that the heterozygous carriers had elevated triglyceride level and reduced insulin sensitivity compared with non-carriers ( $P < 0.0005$  and  $P = 0.014$ , respectively). A meta-analysis including 19 246 individuals showed nominal significant association between LPL N291S (rs268) variant and T2D (odds ratio=2.26, 95% confidence interval (CI): 1.02–4.99,  $P = 0.04$ ) and CHD (odds ratio=1.48, 95% CI: 1.09–2.00,  $P = 0.01$ ). Although not convincing, together with the powerful correlation between significantly decreased catalytic activity (~60% of the wild type) and secretion ability (about 50% of the wild type) of N291S mutant and deleterious lipid profile (triglycerides: 32.3% increase and HDL-C: 34.2% decrease), which are risk factors of T2D and CHD, this association may be not a false-positive result and further study is necessary and justifiable.<sup>24</sup> Goodarzi *et al.*<sup>25</sup> analyzed haplotypes of six polymorphisms in LPL and provided compelling evidence that the LPL gene might have a role in determining insulin sensitivity ( $P = 0.031$ , haplotype 1: GATTCG) and insulin resistance ( $P = 0.007$ , haplotype 4: GAGGGG) in their Mexican-American population. Transgenic (Tg) watanabe heritable hyperlipidemic (WHHL) rabbits that overexpress the human LPL gene were generated by Koike *et al.* In addition to dramatically ameliorating hypertriglyceridemia and hypercholesterolemia, overexpression of LPL was able to suppress high-diet-induced obesity and insulin resistance in these Tg WHHL rabbits.<sup>26</sup> However, two reports<sup>27,28</sup> suggest that overexpression of human LPL in skeletal muscle of mouse could aggravate insulin resistance through the insulin signal cascade. A recent study found that the reduced LPL delivery in skeletal muscle in skeletal muscle-specific LPL knockout mouse (SMLPL $-/-$ ) induced increased insulin sensitivity in skeletal muscle but insulin resistance in other metabolic tissues, and ultimately led to obesity and systematic insulin resistance.<sup>29</sup> These results suggested that systematic overexpression of LPL might improve insulin resistance, although the underlying mechanism is not clear. These controversies suggest that the association between the LPL gene and T2D may be tissue specific. Some results relevant to the underlying mechanisms have been reported as follows: Cruz *et al.*<sup>29</sup> study indicated that more FFA could be delivered to

pancreatic  $\beta$ -cells by increasing LPL activity, consequently impairing  $\beta$ -cell function and promoting apoptosis in the patients with hyperglycemia, hyperinsulinemia and T2D. Hypertriglyceridemia prioritizing the utilization of TAG as fuels inhibits the intake and oxidization of glucose;<sup>27</sup> intracellular fatty acid metabolites interfere with propagation of insulin signaling cascade;<sup>28</sup> and delivering more FFA to pancreatic  $\beta$ -cells impairs  $\beta$ -cell function and promote apoptosis.<sup>29</sup> The above findings may be partly responsible for the association between LPL and T2D.

#### LPL and EH

The occurrence of EH is affected by hereditary and environmental factors and interaction between them.<sup>30</sup> Many previous findings have shown that abnormal lipid metabolism and insulin resistance may have a role in the process of EH. LPL, hydrolyzing TG and regulating lipid metabolism, is logical to be regarded as the candidate gene for EH.

Linkage analysis of 148 Chinese hypertensive pedigrees with seven micro-satellite makers of LPL gene discovered links between systolic blood pressure (SBP) and marker D8S261 (LOD=2.68) and NEFL (LOD=2.1), between diastolic blood pressure (DBP) and marker D8S1145 (LOD=1.06) and NEFL (LOD=1.22) in the region of 8p22 (LPL located on the region); two common mutations *HindIII* (rs320;  $P = 0.004$ ) and *Hinfl* (rs328;  $P = 0.004$ ) in the LPL gene were both associated with DBP.<sup>31</sup> In addition, another quantitative-transmission/disequilibrium test (TDT) also showed significant association between EH and D8S261 ( $P = 0.0002$  and 0.033 for SBP and DBP, respectively).<sup>32</sup> The association of LPL and hypertension was supported by another independent study in the Chinese Han population, indicating that a polymorphism in intron 8 of *PLP* may be a risk variant for EH (OR=2.9,  $P < 0.01$ ).<sup>33</sup> These findings have not been replicated in Caucasian samples<sup>34</sup> and suggest that LPL might have a race-specific role in the development of hypertension. The underlying mechanisms might include the effect of elevated TG on hemodynamics, sodium re-absorption, retention and vascular hypertrophy,<sup>15</sup> and the role of LPL in the regulation of arterial stiffness.<sup>31</sup>

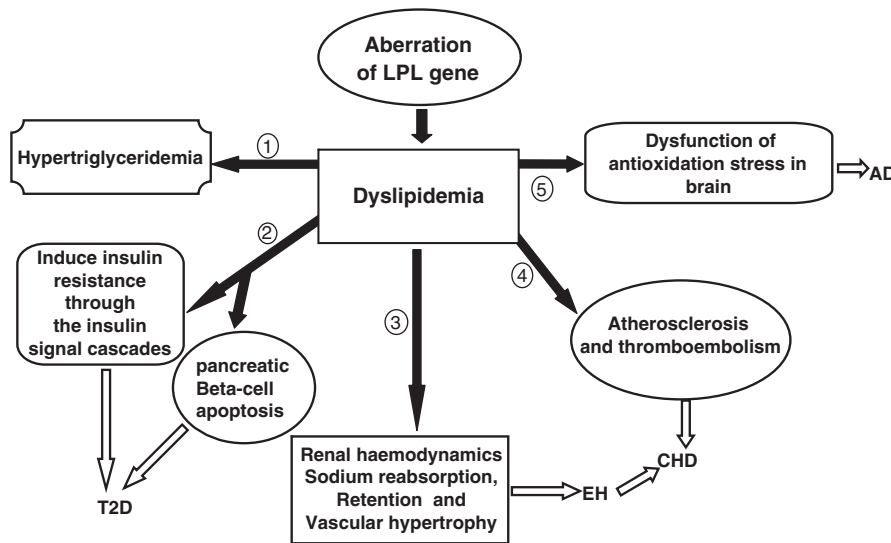
#### LPL and CHD

It is known that insulin resistance and hypertension are independent risk factors for CHD. On the basis of the linkage of the LPL gene to these factors, LPL is a candidate gene for CHD. A study by Socquard *et al.*<sup>35</sup> in 404 unrelated French patients with T2D found

that the prevalence of CHD in this population was 18%, but increased to 29 and 38% in H2H2 (rs320, the site of *HindIII*) and P2P2 (rs285, the site of *PvuII*), respectively, polymorphism carriers at LPL ( $P < 0.02$ ). The findings by Zee *et al.*<sup>36</sup> indicated that LPL N291S (rs268) genetic variant is an independent predictor of increased risk of venous thromboembolism (OR=3.09; 95% CI: 1.56–6.09;  $P = 0.001$ ), also supporting a role for the LPL gene in vascular biology. One study among 2484 inhabitants of the municipality of Hoorn discovered that low LPL activity and high triglyceride concentration are determinants of small LDL size,<sup>37</sup> which is associated with increased risk of cardiovascular disease (CVD).<sup>38</sup> The naturally occurring LPL S447X, which was shown to increase the lipolytic function of LPL and a gain-of-function mutation, could reduce the CVD risk compared with S447S.<sup>39</sup> All of these observations suggest that LPL might involve in the etiology of CHD. However, the underlying mechanism is complicated and tissue specific. Overexpression of LPL in monocyte-derived macrophages (MDM) induces unregulated uptake of NEFA and 2-monoacylglycerol and re-esterified into TAG. The lipid saturated macrophages evolve into foam cells and then penetrate the endothelium cells into the middle layer of vascular wall.<sup>40</sup> In addition, the LPL could trigger other pro-pathogenic events, such as the proliferation of smooth muscle cells.<sup>41</sup> A marked decrease in diet-induced atherosclerosis was detected in chimerical mice that are deficient for macrophage LPL expression,<sup>42</sup> and atherosclerosis was accelerated in transgenic apoE-deficient mice by macrophage-specific expression of human LPL.<sup>43</sup> In the adipose and muscle tissues, however, LPL acts protectively because it aids in the clearance of circulating lipoprotein particles through storage or utilization.<sup>6</sup>

#### LPL and AD

Recently, reports on the association between LPL and AD have increased. No significant distribution difference ( $P = 0.09$ ) of S477X (rs328) is found between 852 patients with AD and 190 healthy controls in Baum *et al.* study,<sup>44</sup> which is supported ( $P > 0.05$ ) by the Fidani *et al.* report.<sup>45</sup> However, Blain *et al.*<sup>46</sup> study (in 153 patients with AD and 242 controls from Canada), on a *PvuII* SNP polymorphism (rs285) of LPL, discovered that homozygote of P+ allele resulted in an odds ratio of 2.3 for the risk of developing AD; the P+ allele could significantly affect its mRNA expression level ( $P = 0.026$ ), brain tissue cholesterol levels ( $P = 0.0013$ ),



**Figure 1** The schematic of the relationships among the lipoprotein lipase (LPL) gene and dyslipidemia, type II diabetes (T2D), essential hypertension (EH), coronary heart disease (CHD) and Alzheimer disease (AD). Dyslipidemia, induced by the aberration of the LPL gene, might be the shared intermediate process on the development of these five diseases. Hypertriglyceridemia features dyslipidemia. Involves in regulating the pancreatic  $\beta$ -cell function,  $\beta$ -cell apoptosis and the insulin signal cascades, which aggravates insulin insufficient secretion and insulin resistance and then induces T2D. Hyperinsulinemia induced by elevated TG, may be partly responsible for EH by its functions on renal hemodynamics, sodium re-absorption, retention and vascular hypertrophy. Elevated TG is associated with atherosclerosis and thromboembolism; both of them are high-risk factors for the development of CHD. *LPL* has a role in the antioxidation stress of brain through lipids scavenging and recycling, regarded as a protective factor for Alzheimer's disease (AD). Dysfunction of antioxidation stress induced by *LPL* aberration, in the brain, might be a risk factor of AD.

neuro-fibrillary tangles ( $P=0.025$ ) and senile plaque ( $P=0.022$ ) densities. In 243 Italian patients with AD and 148 healthy subjects, the H+ allele of *HindIII* SNP (rs320) showed a trend but not strong association with AD, the odds ratio was 2.7 (95% CI: 1.01–7.21;  $P=0.048$ ); in addition, the homozygote of H+H+ genotype could increase the risk of developing AD ( $P=0.029$ ).<sup>47</sup> These discrepancies may be attributed to one of the following reasons. First, it is possible that different ethnic groups may have different risk alleles in the same gene or may have different predisposing genes for AD. Second, it is possible that an independent study with small samples has limited power to detect association of small effect, and is prone to false positives or negatives. Finally, false positives or negatives owing to statistical chance cannot be completely eliminated.

Findings from the neuroblastoma cells suggest that *LPL* expression in neurons stimulates the extension of neuritis and protects the neurons against oxidized lipoproteins toxicity.<sup>48</sup> *LPL* overexpression was found in the lesion brain region in mouse models, and *LPL* mRNA level was upregulated in microglial cells during ischemia produced by occlusion of the middle cerebral artery, and was involved in the scavenging and recycling of

lipids by microglial cells in the brain.<sup>49,50</sup> Thus, *LPL* secreted by microglial cells may not only help in the recycling of lipids but could also potentially act as a trophic factor for neuronal survival and differentiation. AD is considered as a neurodegenerative disease, however, and multiple pieces of evidence show that oxidative stress may also have a pathogenic role in AD.<sup>51</sup> These results suggest that *LPL* might have a role in the antioxidation stress of brain through lipids scavenging and recycling, bonding function and other unrecognized mechanisms, and indicate that *LPL* may be a protective factor of AD. Therefore, dysfunction of antioxidation stress induced by *LPL* aberration, in the brain, might be a risk factor of AD. More investigations of genetics and biology are required to confirm the association between *LPL* and AD, and to uncover the mechanism of *LPL* underlying AD.

## DISCUSSION

We have shown the existence of a common biological basis for several common complex diseases. The examples given here support the idea that *LPL* is involved in several diseases such as dyslipidemia, T2D, EH, CHD and AD. Hypertriglyceridemia, T2D, EH, CHD and AD, all display dyslipidemia in the initial

stage or throughout their whole pathological process. Owing to the lipolytic function of *LPL*, it was considered a good candidate gene for these diseases. Catalytic function of *LPL* is the main basis in these relationships, deficient synthesis or dysfunction of *LPL* reduces hydrolysis of chylomicron and VLDL, hindering intake of lipids, and eventually resulting in redundant accumulation of lipoproteins in the plasma.<sup>6</sup> The antioxidation stress function of *LPL* promotes clearance of the lipid remnants from the circulation, which are re-esterified for storage and utilization in tissues.<sup>7–10,48–50</sup> Dyslipidemia, induced by the aberration of the *LPL* gene, might be the shared intermediate process on the development of these five diseases. The hypertriglyceridemia could directly be induced by the dysfunction of *LPL*. However, T2D, EH, CHD and AD are indirectly associated with *LPL* by different patho-physiological mechanisms and signal pathways (see Figure 1). According to the findings reported here, we surmise that *LPL*'s antioxidation stress may be one important mechanism underlying the etiology of T2D, EH, CHD and AD, but more research is required to elucidate this. Therefore, dyslipidemia and dysfunction of antioxidation stress induced by aberration of *LPL* gene might be two risk factors for the development of T2D, EH, CHD and AD.

Although evidence from the *LPL* gene studies supports the hypothesis that there is a common biological basis for the common complex diseases, a number of questions have also arisen from these studies that need to be investigated in more detail. First, the molecular mechanisms that potentially link *LPL* to T2D, EH, CHD and AD need specific attention in future research. Second, even for a widely examined polymorphism, such as S447X (rs328), reports from different ethnic samples are not consistent and studies based on large and well-matched samples are required. Third, as described in this review, tissue/cell-specific regulation of *LPL* has a major implication for diseases, such as T2D and CHD; and this selective modulation of *LPL* function is important for understanding its pathological mechanism and finding new therapeutic techniques. Fourth, an interesting issue for the future studies is whether or not *LPL* might have a part in the development of other diseases such as schizophrenia.<sup>52</sup>

In short, evidence from these studies of *LPL* are consistent with that from Rzhetsky *et al.*<sup>53</sup> support the idea that separate genetic diseases can overlap in their pathogenesis, especially for diseases that share similar clinical phenotypes. As phenotypic overlap

is a good predictor of functional relatedness of the underlying susceptibility genes or molecular mechanisms,<sup>54</sup> these results indicate that one gene associated with multiple diseases might exist in the population and this phenomenon should be considered as a network of interrelated diseases and disease traits, rather than a list of distinct disease entities.<sup>55</sup> The detailed and accurate exploration of this interesting and important hypothesis should be helpful for elucidating the etiology of common complex diseases, and has a potential impact on the study for liability genes of complex human diseases.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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