The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Editorial

J Atheroscler Thromb, 2020; 27: 1255-1256. http://doi.org/10.5551/jat.ED133

Polygenic Architecture of Common Severe Hypertriglyceridemia

Takashi Yamamoto and Takanari Gotoda

Department of Metabolic Biochemistry, Faculty of Medicine, Kyorin University, Tokyo, Japan

Key words: **Exome, Next-generation sequencing, Mutation, Gene variant, Type V hyperlipidemia**

See article vol. 27: 1264-1277

Severe hypertriglyceridemia usually accompanies hyperchylomicronemia and is classified into types I and V hyperlipidemia characterized by an increase in chylomicrons alone and an increase in both chylomicrons and very-low-density lipoproteins (VLDLs), respectively[1]. The extremely rare, monogenic form of hyperchylomicronemia is often referred as familial chylomicronemia syndrome (FCS) that usually manifests as type I hyperlipidemia during childhood or adolescence[2]. The genetic basis of FCS has been extensively investigated, revealing that the primary underlying causes common to FCS are critical defects in the lipolytic function of lipoprotein lipase (LPL), a crucial rate-limiting enzyme for hydrolysis of triglycerides (TG) in both chylomicrons and VLDLs[3]. Accordingly, monogenic, recessive disease-causing mutations have been found in *LPL* itself or other genes essential for LPL function (such as *APOC2*, *APOA5*, *GPIHBP1*, and *LMF1*) in the majority of FCS patients[4].

Although FCS is a very rare clinical condition that is found in approximately 1~10 patients in a million people, severe hypertriglyceridemia can be more frequently experienced in general clinics or hospitals, typically in adult patients with type V hyperlipidemia. The predisposition to type V hyperlipidemia seems more complex genetically and more likely to be influenced by secondary environmental factors compared with type I hyperlipidemia[5]. Although previous results have clearly revealed the excess of the presence of heterozygous critical mutations or rare gene variants identified by genome-wide association studies in patients with severe hypertriglyceridemia[6, 7], more detailed analysis with next-generation sequencing is limited.

In this issue of Journal of Atherosclerosis and Thrombosis, Matsunaga *et al.* report the results of a genetic analysis of 23 adult Japanese patients with severe hypertriglyceridemia (fasting plasma TG > 1,000 mg/dL, mostly type V hyperlipidemia), focusing on 49 candidate genes with whole-exome sequencing[8]. Differently from the patients with monogenic FCS, none of these study patients had homozygous or compound-heterozygous critical mutations in single gene such as the genes essential for LPL function mentioned above. Furthermore, although six patients (26%) were heterozygous for rare, possibly deleterious gene variants, the pathogenicity of those variants seems much less than that seen in FCS. Besides these six patients, additional sixteen patients (70%) were homozygous or heterozygous for common, possibly deleterious gene variants, whereas only one patient (4%) had none of those gene variants[8] **(Fig. 1)**. Unfortunately, the study by Matsunaga *et al.* fails to include normal control population. Nevertheless, compared with the allelic frequencies among the general Japanese population derived from the Human Genetic Variation Database, it seems evident that not only such rare gene variants but also most common gene variants have been over-represented in Japanese patients mostly with type V hyperlipidemia.

Recently, a similar but much larger-scale study has been reported in Caucasian patients from European descent. The study by Dron *et al.*[9] included 563 patients with severe hypertriglyceridemia and focused on 73 genes by targeted next-generation sequencing as well as on 185 single-nucleotide polymorphisms associated with dyslipidemia. Among these patients, 1.1% had biallelic (homozygous or compound-heterozygous) rare variants, 14.4% had heterozygous rare variants, and 32.0% had an extreme accumulation of

Address for correspondence: Takanari Gotoda, Department of Metabolic Biochemistry, Faculty of Medicine, Kyorin University, 6-20-2 Shinkawa, Mitaka-city, Tokyo, Japan. 181-8611. E-mail: gotoda@ks.kyorin-u.ac.jp
Received: April 19, 2020 Accepted for publication: April 20, 2020

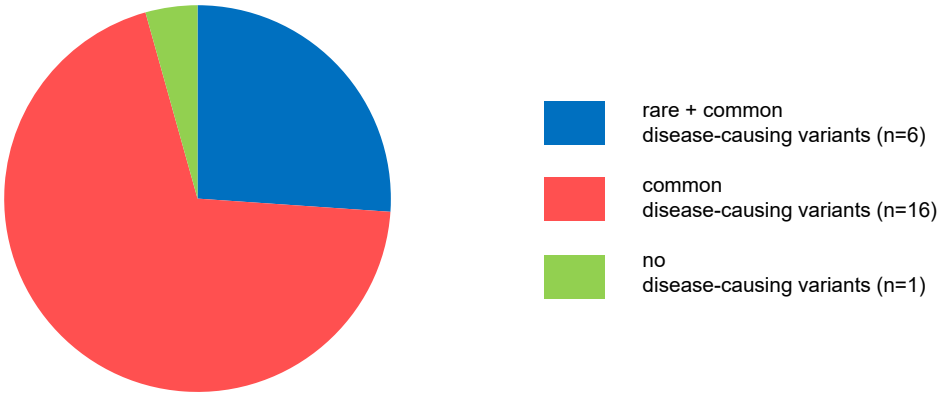

Fig.1.

Distribution of the rare (<1% allele frequency) and common (>1%) disease-causing gene variants identified by Matsunaga *et al.* in 23 Japanese patients with severe hypertriglyceridemia (fasting TG >1,000 mg/dL, 11.29 mmol/L). The disease-causing variants were those identified by in silico predictions or reported previously of pathogenic significance (see text)[8].

common variants[9]. Although the fundamental study design was not identical, taken together, the studies by Matsunaga *et al.*[8] and Dron *et al.*[9] indicated that the over-representation of both rare and common pathogenic gene variants is a common predominant feature of severe hypertriglyceridemia, especially of type V hyperlipidemia, beyond the ethnical differences. In addition, it seems important to point out that about 40% of the patients had diabetes mellitus in either of the two studies and 74% consumed alcohol in the study by Matsunaga *et al.*, which emphasizes the great influences by the secondary environmental factors. More comprehensive understanding of the polygenic architecture as well as the gene—environmental interaction will facilitate the development of better diagnostic and therapeutic measures for severe hypertriglyceridemia.

Conflicts of Interests

None.

References

1) Fredrickson DS and Lees RS: Familial hyperlipoproteinemia. in The Metabolic Basis of Inherited Disease (ed. by Stanbury JB, Wyngaarden JB and Fredrickson DS), 2nd ed., New York, McGraw-Hill, 1966, pp429
2) Brown WV, Gaudet D, Goldberg I and Hegele R: Roundtable on etiology of familial chylomicronemia syndrome. J Clin Lipidol, 2018; 12: 5-11
3) Brunzell JD and Deeb SS: Familial lipoprotein lipase deficiency, apoC-II deficiency and hepatic lipase deficiency. in The Metabolic and Molecular Bases of Inherited Disease (ed. by Scriver CR, Beaudet AL, Sly WS, Valle D, Childs B, Kinzler KW and Vogelstein B), 8th ed., New York, McGraw-Hill, 2000, pp2789-2816
4) Surendran RP, Visser ME, Heemelaar S, Wang J, Peter J, Defesche JC, Kuivenhoven JA, Hosseini M, Péterfy M, Kastelein JJ, Johansen CT, Hegele RA, Stroes ES, and Dallinga-Thie GM: Mutations in LPL, APOC2, APOA5, GPIHBP1 and LMF1 in patients with severe hypertriglyceridaemia. J Intern Med, 2012; 272: 185-196
5) Gotoda T, Shirai K, Ohta T, Kobayashi J, Yokoyama S, Oikawa S, Bujo H, Ishibashi S, Arai H, Yamashita S, Harada-Shiba M, Eto M, Hayashi T, Sone H, Suzuki H and Yamada N: Diagnosis and management of type I and type V hyperlipoproteinemia. J Atheroscler Thromb, 2012; 19: 1-12
6) Wright WT, Young IS, Nicholls DP and Graham CA: Genetic screening of the LPL gene in hypertriglyceridaemic patients. Atherosclerosis, 2008; 199: 187-192
7) Johansen CT, Wang J, Lanktree MB, Cao H, McIntyre AD, Ban MR, Martins RA, Kennedy BA, Hassell RG, Visser ME, Schwartz SM, Voight BF, Elosua R, Salomaa V, O'Donnell CJ, Dallinga-Thie GM, Anand SS, Yusuf S, Huff MW, Kathiresan S and Hegele RA: Excess of rare variants in genes identified by genome-wide association study of hypertriglyceridemia. Nat Genet, 2010; 42: 684-687
8) Matsunaga A, Nagashima M, Yamagishi H and Saku K: Variants of lipid-related genes in adult Japanese patients with severe hypertriglyceridemia. J Atheroscler Thromb, 2020; 27: 1264-1277
9) Dron JS, Wang J, Cao H, McIntyre AD, Iacocca MA, Menard JR, Movsesyan I, Malloy MJ, Pullinger CR, Kane JP and Hegele RA: Severe hypertriglyceridemia is primarily polygenic. J Clin Lipidol, 2019; 13: 80-88