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. 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. The genetic basis of FCS has been extensively investigated, revealing that the primary underlying cause 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. 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.

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. 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, 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. 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%) had an extreme accumulation of common gene variants, whereas only one patient (4%) had none of those gene variants (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. 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
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.

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