The Molecular Basis of Severe Hypertriglyceridemia: From Genetic Counseling to Gene Therapy

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Severe hypertriglyceridemia (fasting triglycerides above 1000 mg/dl) is a common condition that occurs in 1:600 individuals [1]. Clinical features include hepatomegaly, eruptive xantomatosis, lipemia retinalis and pancreatitis [2]. Hypertriglyceridemia also increases the risk of cardiovascular disease [3]. Genetic susceptibility to hypertriglyceridemia is now elucidated. Extreme hypertriglyceridemia is less common and is caused by a simple monogenic disorder showing a typical Mendelian recessive inheritance presenting in early childhood and resulting from homozygosis for large-effect genetic mutations.

Lipoprotein lipase is the enzyme responsible for lipolysis of triglyceride-rich lipoproteins [4]. More than 70 mutations are known in the LPL gene, causing about half the cases of extreme hypertriglyceridemia [5]. In this issue of IMAJ Behar and co-authors [6] report the detection of such a mutation in the LPL gene using the available tools of modern genetics and sequencing the LPL genes of the proband and his family. Other genes causing the same phenotype include Apo protein C-II (Apo cII), lipase maturation factor 1 (LFMI), glycosylphosphatidylinositol-anchored high density lipoprotein binding protein 1 (GPIHBPI) and apoprotein A5 (APO5) [7]. The accurate diagnosis of the genetic cause in a specific family is now feasible and enables detection of novel mutations in candidate genes, as shown by Behar et al. in their current report [6].

Another group is Israel used a similar approach to detect a mutation in the gene encoding glycerol 3 phosphate dehydrogenase 1 in two Arab Israeli families, which explains the phenotype of severe hypertriglyceridemia and fatty liver [8]. While accurate genetic counseling is very important, new modalities of therapy are now becoming feasible. At least one of the mutations in the LPL gene is a gain-of-function mutation (s447x). The presence of this variant enables better LPL enzyme activity and lowers triglyceride levels [9].

Several studies in humans have demonstrated that intramuscular injections of the LPL gene using an adenoviral-associated vector as the vehicle for the normal LPL enzyme and corrects the LPL-deficient status of individuals born without LPL activity due to loss-of-function mutations in the LPL gene. This is believed to be a lasting gene implantation and these patients have a significant reduction in triglyceride levels [10]. In summary, recent advances in genetics have given us a powerful tool for the detection of large-effect monogenic alleles responsible for extreme phenotypes of hypertriglyceridemia and open the door for future gene therapy.

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References

“We hang the petty thieves and appoint the great ones to public office”

Aesop (620-560 BC), Greek storyteller credited with a number of fables now collectively known as Aesop’s Fables. Although his existence remains uncertain, numerous tales credited to him were gathered across the centuries and in many languages in a storytelling tradition that continues to this day. In many of the tales, animals speak and have human characteristics