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 (*LFM1*), glycosylphosphatidylinositol-anchored high density lipoprotein binding protein 1 (*GPIHBP1*) 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* gene prompts production of active 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 monogenetic alleles responsible for extreme phenotypes of hypertriglyceridemia and open the door for future gene therapy.

LPL = lipoprotein lipase

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"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