

Genetic Predisposition of Human Plasma Triglyceride Concentrations

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Summary

The issue of plasma triglyceride levels relative to the risk of development of cardiovascular disease, as well as overall mortality, has been actively discussed for many years. Like other cardiovascular disease risk factors, final plasma TG values have environmental influences (primarily dietary habits, physical activity, and smoking), and a genetic predisposition. Rare mutations (mainly in the lipoprotein lipase and apolipoprotein C2) along with common polymorphisms (within apolipoprotein A5, glucokinase regulatory protein, apolipoprotein B, apolipoprotein E, cAMP responsive element binding protein 3-like 3, glycosylphosphatidylinositol-anchored HDL-binding protein 1) play an important role in determining plasma TG levels.

Key words

Triglycerides • Polymorphism • Mutation • Predisposition

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Introduction

Elevated plasma triglyceride (TG) concentration has repeatedly been found to be a strong independent risk factor for cardiovascular disease (Cullen 2000, Forrester 2001, Labreuche 2009) and is an important and independent predictor of all-cause mortality across all ethnicities (Zilversmit 1976, Liu *et al.* 2013, Pikhart *et al.* 2015). In the plasma, TGs circulate as a part of the

following lipoprotein particles: chylomicrons, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), and remnants of these (Karpe 1999). TG and cholesterol esters represent the core of the particle, along which lipoproteins form a layer of phospholipids, apolipoproteins, and unesterified cholesterol. After meal ingestion, chylomicrons are formed in the small intestines and VLDL particles carrying endogenously synthesized TG originate in the liver (Hassing 2012). TGs carried by these lipoprotein particles are hydrolyzed by lipoprotein lipase (LPL) into monoacylglycerol and two free fatty acids on the luminal surface of endothelial cells in capillaries within adipose and muscle tissues (Mead *et al.* 2002).

Hypertriglyceridemia (HTG) is diagnosed on the basis of TG plasma levels elevated above the threshold value of 1.7 mmol/l (Reiner *et al.* 2011); severe hypertriglyceridemia is usually defined as TG plasma concentrations greater than 10 mmol/l. Compared to cholesterol concentration, plasma TG levels can vary widely (Boullart *et al.* 2012). From family and linkage studies, it has been estimated that genetic factors can explain 30-70 % of the overall TG concentration.

Monogenic hypertriglyceridemia

Monogenic HTG is an autosomal recessive disorder; patients are either homozygotes or compound heterozygotes with loss-of-function (LOF) mutations in the genes that encode the proteins involved in the catabolism of lipoprotein particles carrying high proportions of TGs (Johansen *et al.* 2011a, Johansen and

Hegele 2011). However, the genetic nature is much more complex in the majority of familial HTG cases. Carriers with identical mutations can manifest with a wide spectrum of phenotypes ranging from normotriglyceridemia to severe HTG (Babirak *et al.* 1989, Hegele *et al.* 1991). This may be a consequence of variability in the number of common variants that can elevate plasma TG levels.

The monogenic form of HTG is present in populations with frequencies as rare as one in one million; or (due to genetic drift) as common as 1 in 40 in specific Canadian populations (Gagne *et al.* 1989, Johansen and Hegele 2012a). It frequently manifests in patients during childhood or adolescence, with signs such as cutaneous eruptive xanthomata, lipemia retinalis, failure to thrive, recurrent epigastric pain, hepatosplenomegaly, pancreatitis, and focal neurologic symptoms (Brahm and Hegele 2013). It is characterized by TG concentrations above the 99th percentile as a result of plasma chylomicrons concentration elevations that persist during the fasting state (Johansen and Hegele 2012a, Brahm and Hegele 2013).

Examples of monogenic hypertriglyceridemias

Lipoprotein lipase

Monogenic HTG is most frequently caused by mutations in the *LPL* gene, a member of the lipase gene family on the short arm of chromosome 8. The *LPL* gene consists of 10 exons that encode a 475 amino acid (aa) protein (Mead *et al.* 2002). The main function of the LPL protein is hydrolysis of TG transported in chylomicrons and VLDL particles. Hydrolysis produces monoacylglycerol and 2 molecules of free fatty acids that can be stored in adipose tissue or used during beta-oxidation (energy source) in skeletal and heart muscle tissue (Cryer 1981). LPL action takes place on the luminal surface of endothelial cells in capillaries, where it is held in place by heparan sulphate proteoglycans (Braun and Severson 1992); however, it can also dissociate from endothelial tissue and continue lipolytic activity in the bloodstream (Goldberg 1996). After glycosylation in the endoplasmic reticulum, LPL is secreted from parenchymal cells as a homodimer (Mead *et al.* 2002). The exact release mechanism is still unknown; however, glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1 (GPIHBP1, see below) is required for transport to the vascular lumen (Johansen and Hegele 2012a). N-terminal domain mutations are reported to attenuate catalytic activity of LPL, while

mutations associated with the carboxyl terminus prevent binding to GPIHBP1 (Voss *et al.* 2011). Currently, the HGMD database lists 123 missense/nonsense, 11 splicing, 6 regulatory, 33 deletion/insertion/indel mutations, 5 large deletion/insertion mutations, and 1 complex rearrangement mutation. The most deleterious missense mutations, which cause loss of function, are located in the highly conserved catalytic domain. These mutations in heterozygous state (e.g. p.Gly161Glu, p.Val206Ala within exon 4 and 5) lead to significant elevation of plasma TG (Surendran *et al.* 2012) despite the expectation of milder phenotypic expression in heterozygotes (Rahalkar *et al.* 2009). A mutation in the initiation codon of the *LPL* gene has been described in a patient with severe HTG and recurrent pancreatitis (Met1Ile). The mutation led to a 98 % reduction in protein activity as a result of reduced expression (Yu *et al.* 2006). Different LPL activity levels have been demonstrated for several of the different variants within the promoter region of the *LPL* gene. While substitutions at positions -79 and -95 did not change promoter activity at all, there was an 85 % reduction associated with a T(-39)C substitution, a 70-75 % reduction associated with G(-53)T, a 40-50 % reduction associated with T(-93)G, and a 20-50 % reduction associated with a CC insertion at position -95 (HGMD) (Yang *et al.* 1996).

Apolipoprotein C2

Other genes involved in activity regulation, transport, assembly, and binding of LPL can also play a role in the development of HTG. A product of one of these, apolipoprotein C2 (APOC2), is a component of lipoprotein particles. It has been shown to be an essential cofactor and activator of LPL activity (Scanu 1966). Biallelic loss-of-function mutations in the *APOC2* gene can cause APOC2 deficiency leading to extremely high levels of plasma TG (Talmud 2001). This extremely rare autosomal recessive disease develops at a later age and patients suffer from chronic pancreatic insufficiency with steatorrhea and insulin-dependent diabetes mellitus (Brunzell and Deeb 2001, Deeb 2013). The *APOC2* gene has been localized to the long arm of chromosome 19 as a part of the *APOE-C1-C4-C2* gene cluster. *APOC2* consists of four exons encoding a 79 aa protein (Kei *et al.* 2012). The N-terminus carries the lipid-binding domain, which has no effect on LPL activity (Wang 1991), while the C-terminal helix acts as an LPL activator (Musliner *et al.* 1979). The most important residue is leucine 72, which directs lipids to the LPL active site in cooperation with other, evolutionary highly conserved, hydrophobic

residues (Shen *et al.* 2002, Lam *et al.* 2006). The *APOC2* gene is mainly expressed in the liver, and minor expression has also been demonstrated in the intestines and pancreas (Zannis *et al.* 1985, Lenich *et al.* 1988). Two control regions have been found in the *APOE-C1-C4-C2* gene cluster, each of which, under different experimental conditions, can dominate *APOC2* control (Allan *et al.* 1997, Vorgia *et al.* 1998). There are few causal mutations described for this gene; i.e. 10 missense/nonsense and 2 splicing mutations, 1 regulatory mutation, 4 small deletions/insertions, and 2 gross deletions (HGMD). Generally, the mutations either prevent efficient production of the *APOC2* protein (Fojo *et al.* 1988, 1989, Okubo *et al.* 1997, Nauck *et al.* 1998, Chen *et al.* 2007), or produce nonfunctional and/or proteins with low activity (Connelly *et al.* 1987, Inadera *et al.* 1993). Interestingly, in transgenic mice, a positive correlation has been found between elevated TG and apoC2 plasma concentrations, which is expected to be (at least in part) a causal relationship (Shachter *et al.* 1994).

Lipase maturation factor 1

LPL undergoes maturation in the endoplasmic reticulum during its development. A protein carrying an evolutionary highly conserved domain on its C-terminus plays an essential role in this maturation process (Peterfy *et al.* 2007). Homozygous carriers of mutations in the gene encoding this protein (i.e. the lipase maturation factor 1 (*LMF1*) gene) are unable to produce functional LPL despite sufficient plasma concentrations or the absence of any defects in the *LPL* gene itself, which leads to extremely high plasma TG concentrations (Peterfy *et al.* 2007). Heterozygotes have normal plasma TG levels. The *LMF1* gene is located on the short arm of chromosome 16 and has 11 exons encoding a 567 aa protein. So far, all medically detected important variants (N=11) are characterized as missense/nonsense mutations (HGMD). Interestingly, a terminating mutation at position c.1319 C>G (Tyr439X) completely prevents functional maturation of LPL (Peterfy *et al.* 2007), while the c.1389G>A (Trp464X) mutation decreases efficiency of the maturation process by 60 % (Cefalu *et al.* 2009). An adjacent C-loop domain serves as a dimeric lipase specific binding site. It was shown to be the most conserved region of the gene, and probably interacts physically with the C-terminal domain; however, its role in lipase maturation is unknown (Doolittle *et al.* 2010). The functional importance of the N-terminus was recently revealed, when it was observed that the N-truncated

protein does not promote lipase maturation (Babilonia-Rosa and Neher 2014).

Glycosylphosphatidylinositol-anchored HDL-binding protein 1

Glycosylphosphatidylinositol-anchored HDL-binding protein 1 (GPIHBP1) is located on the luminal surface of capillary endothelium in the heart, skeletal muscle, and adipose tissue (Beigneux *et al.* 2007). The functions of this protein include: (1) serving as a platform for LPL and its substrates in order to increase efficiency of hydrolysis, (2) being required for transport of LPL from its secretion site, i.e. parenchymatic cells, to the luminal surface of capillaries (Davies *et al.* 2010, Weinstein *et al.* 2010), (3) stabilizing LPL under certain circumstances (Sonnenburg *et al.* 2009), and (4) being involved in cholesterol transport (Ioka *et al.* 2003, Beigneux *et al.* 2007). The gene encoding this 184 aa protein is located on the long arm of chromosome 8, and consists of 4 exons. Sixteen missense/nonsense mutations, one small, and two gross deletions, have been described for this gene (HGMD). It has recently been revealed that only GPIHBP1 monomers are capable of binding to LPL, and the mutations within the Ly6 domain lead to production of di- and/or multimers that are unable to bind LPL. However, the Trp109Ser mutation does not cause multimerization, despite the reduced ability to bind LPL. This suggests that position may play a direct role in LPL binding (Beigneux *et al.* 2015). A polymorphism in the *GPIHBP1* gene promoter (g.-469G>A, rs72691625) has been associated with hypertriglyceridemia, especially in homozygotes, with a significant additive effect when in the presence of the loss-of-function mutation within the *LPL* gene (Guay *et al.* 2013). On the other hand, the *LPL* polymorphism that results in Ser447X, which shortens LPL by two amino acids and has been associated with low plasma TG levels, has been experimentally shown to have the same, binding efficiency relative to normal LPL (Turlo *et al.* 2014).

Apolipoprotein A5

The suggested function of apolipoprotein A5 is facilitation of the interaction between heparan sulfate and *APOC2* on TG-rich lipoproteins and the interaction of *APOC2* with LPL on the surface of vascular endothelium (Nilsson *et al.* 2008). Experiments using mice have shown an increase in plasma TG concentrations in *apoA5*-knockout animals, and a decrease in plasma TG concentration as a consequence of *APOA5* overexpression (Pennacchio *et al.* 2001). The human

APOA5 gene is part of the *APO A1-A4-C3-A5* cluster, which is located on the long arm of chromosome 11. It consists of four exons encoding a 366 aa protein, with 23 of these serving as a signal peptide (Pennacchio *et al.* 2001). Several rare mutations have been described, i.e. 46 missense/nonsense, five splicing, 4 regulatory mutations, 9 small deletions/insertions, and 2 gross rearrangements (HGMD). They usually occur within one family tree only, and carriers have a very wide range of plasma TG concentrations.

Common variants of apolipoprotein A5 (*APOA5*) strongly affect plasma TG levels. Heterozygotes with variants in the *APOA5* gene show high variability in plasma TG levels, and although a significant number have TG levels within the normal range, this variability is generally higher than in homozygotes. Most *APOA5* polymorphisms involve linkage disequilibrium and haplotypes can be easily distinguished by analysis of the rs662799 and rs3135506 variants (Guardiola *et al.* 2015).

The effect of the most commonly analyzed substitution (C-1131>T, rs662799) was reviewed in a publication from the Triglyceride Coronary Disease Genetics Consortium and Emerging Risk Factors Collaboration (2010). The review confirmed that one minor allele is associated with approximately 15 % higher plasma TG levels and significantly increased risk of cardiovascular disease.

Another single nucleotide polymorphism (SNP) consistently associated with elevated plasma TG concentrations (c.56G>C, Ser19Trp, rs3135506) has also been found in different ethnicities and the effect on plasma TG is similar to the rs662799 variant in Caucasians (Hubacek 2005).

The minor variant allele (rs2266788) in 3'UTR has been shown to have a strong association with elevated plasma TG levels, both alone and as a part of *APOA5* haplotype 2 (Pennacchio *et al.* 2002, Elosua *et al.* 2006, Garelnabi *et al.* 2013). The same allele can either create or destroy the binding site of different miRNAs. For microRNA 3201, its binding causes a delay in *APOA5* mRNA degradation, and increases the plasma concentration of this messenger RNA. Destruction of the binding site leads to a decrease in *APOA5* mRNA concentration and consequently decreases protein production (Cui *et al.* 2014). This allele also creates a binding site for miRNA miR-485-5p, which prevents efficient expression of the protein (Caussy *et al.* 2014).

Two polymorphisms (rs662799 and rs651821)

have been found to increase plasma TG levels and were associated with higher risk of obesity and higher non-HDL-cholesterol plasma levels in Chinese children (Zhu *et al.* 2014). Pullinger *et al.* (2008) reported a higher prevalence of the c.553G>T substitution within this gene among hypertriglyceridemic Asians relative to controls. This variant has not been detected in Caucasians, Hispanics or African Americans (Pennacchio *et al.* 2002).

Polygenic hypertriglyceridemia

Familial hypertriglyceridemia is a result of multiple genetic and environmental factors rather than strictly being a monogenic disease. Accumulation of common DNA variants having relatively little effect, and rare variants that produce large effects, both contribute to the development of the disease. The course of the disease is further exacerbated by environmental and life-style factors such as being overweight, alcohol intake, and food composition (Yuan *et al.* 2007). While genetic factors play a mutual role in primary hypertriglyceridemias, secondary HTG arises as a consequence of external factors or other health conditions, such as diabetes, acute alcohol intoxication, acute pancreatitis, gout, gram-negative sepsis, glycogen storage disease I, and oral contraceptive use (Segen 1992).

The genetic nature is highly complex in the majority of familial HTG cases. For example, studies of parents of individuals suffering from complete inactivation of LPL and/or APOC2, or heterozygous carriers of loss-of-function mutations in respective genes, showed a wide spectrum of phenotypes ranging from normotriglyceridemia to severe HTG (Babirak *et al.* 1989, Hegele *et al.* 1991). This may be a consequence of variability in the number of common variants that can elevate plasma TG levels.

Apolipoprotein E

Apolipoprotein E (*APOE*) is an extensively studied example of the context dependent modulating effect of genetic polymorphism (Hubacek and Vrablik 2011). APOE is a protein component of VLDL and HDL particles with three common isoforms (E2, E3 and E4) that are defined by two SNPs (rs429358 and rs7412), each differing by a single amino acid. APOE2 differs from the more common APOE3 isoform by an Arg158>Cys change, and APOE4 by a Cys112>Arg replacement. APOE variability is associated with plasma cholesterol levels (with APOE4 causing higher, and

APOE2 causing lower, plasma cholesterol levels for its carriers); however, an association with plasma TG levels has been reported as well. Both *APOE2* and *APOE4* alleles have been shown to be associated with higher plasma TG levels which can be influenced by environmental factors, gender, hormonal status, etc. (Frikke-Schmidt *et al.* 2000). In light of recent findings regarding the accumulation of deleterious/protective alleles in individual genomes (Wang *et al.* 2008, Hegele 2009, Johansen and Hegele 2012a), the modulating effect of genetic background may be shown to be real, as previously expected (Reilly *et al.* 1992, Davignon 1993, Fullerton *et al.* 2000).

Moreover, among carriers of the generally beneficial *APOE2E2* genotype (with the resulting beneficial lipid spectrum), about 5 % of individuals develop familial dysbetalipoproteinemia (type III dyslipidemia), which is a disorder with markedly elevated plasma TG levels (Smelt and de Beer 2004). Similar dyslipidemic patterns are very often associated with rare *APOE* mutations (most of which were summarized by Hubacek *et al.* 2000).

In addition to the most studied *APOE2*, *E3*, *E4* polymorphisms, there are at least 23 different variable sites associated with the *APOE* gene; combinations of which give 31 haplotypes. These haplotypes were analyzed in a study designed to unravel the evolutionary history of the *E2*, *E3*, and *E4* alleles (Fullerton *et al.* 2000, Nickerson *et al.* 2000). The results showed that *APOE4* was the ancestral allele and the origin of the *E2* and *E3* alleles was derived, as well as the recent (within the last 60,000 years) increase in the *E3* allele frequency, whose origin is estimated to be 200,000 years ago. However, the interpretation of the observed variability is rather ambiguous due to the modulating influence of genetic background on the effect of each specific variable site, and the extent of causative selective pressures on polymorphisms within the *APOE* gene still remains to be unveiled (Eisenberg *et al.* 2010, Fullerton *et al.* 2000). There is also a possible association *via* linkage disequilibrium as illustrated by the following example of apolipoprotein CI.

Apolipoprotein CI

Next to the *APOE* gene, on chromosome 19, is the gene for APOCI. The product of this gene is a constituent of TG rich lipoproteins and it interacts with most lipoprotein receptors. A polymorphism (4-bp insertion at position -317) with a very tight linkage to

APOE polymorphisms has been described within the promoter region of this gene (Xu *et al.* 1999). The *APOCI* insertion allele is mainly associated with the *APOE2* and *APOE4* alleles, and the common *APOCI* deletion allele is associated with *APOE3*. It is possible that the pattern observed in *APOE* variants relative to plasma TG levels could, in fact, reflect the modulating effect of *APOCI*, since the highest plasma TG levels occur in homozygous carriers with the insertion allele (Hubacek *et al.* 2003).

Genome wide association studies

There is a substantial list of “new” genes, which have been detected by genome wide association studies (GWAS) that significantly impact plasma TG levels. Interestingly, the functions of most of these genes were unknown at the time of discovery (summarized by Vrablik and Hubacek 2010). Despite the power of GWAS, some gene functions were never confirmed by later studies (for example see Kooner *et al.* 2008, Vrablik *et al.* 2008, Polgár *et al.* 2010).

Among these newly emerging genes, the strongest association with plasma TG levels has been shown for the glucokinase regulatory protein (GCKR) gene that encodes a glucokinase inhibitor acting on the liver and pancreatic islet cells by forming an inactive complex with the enzyme. GCKR responds to increased glucose concentrations within cells, and is responsible for glucose phosphorylation at the beginning of the glycolysis process (Orho-Melander *et al.* 2008, Wang *et al.* 2008, Johansen and Hegele 2012a). Initially, associations between plasma TG levels and rs780094 were observed (Orho-Melander *et al.* 2008, Wang *et al.* 2008, Bi *et al.* 2010). Fine-mapping has found an even stronger association between plasma TG levels and the common missense variant rs1260326, in which leucine is substituted for proline at 446 (Orho-Melander *et al.* 2008).

Another recently emerging locus associated with TG levels is *TRIB1*, a gene encoding scaffolding protein tribbles-1, which has been shown to be responsible for modulation of mitogen-activated protein kinase activity and signal transduction related to toll-like receptors (Johansen and Hegele 2012a,b). It is highly expressed in the liver, where it functions as a modulator of VLDL secretion (Burkhardt *et al.* 2010) through regulation of lipid availability (Bauer *et al.* 2009). A polymorphism within this gene (rs2954029) is one of the 32 SNPs

included in HTG-polygenic score (Table 1).

APOB, a well-known locus playing a role primarily in LDL-cholesterol metabolism, has been shown to be associated with plasma TG levels through missense variant Ser4338Ile (rs1042034) in normolipidemic subjects (Hegele 2009). Furthermore, HTG has been associated with another variant located upstream to the *APOB* gene (rs 4635554; Hegele 2009).

An accumulation of eleven mutations in a set of 449 hypertriglyceridemic individuals in comparison to only one among 327 healthy controls was demonstrated for the *CREB3L3* gene, which encodes the cAMP responsive element binding protein 3-like 3 (in the small intestine) and liver-specific mammalian transcription factor CREB-H (Lee *et al.* 2011, Lee 2012). The protein is located in the endoplasmic reticulum and has been linked to acute inflammatory responses (Zhang *et al.* 2006), control of iron absorption (Vecchi *et al.* 2009), and gluconeogenesis (Lee *et al.* 2010). The role of CREB-H in TG metabolism has recently been uncovered; it was found to facilitate TG clearance from plasma *via* induction of LPL coactivators such as ApoA4, ApoA5, and ApoC2 (Lee 2012, Song *et al.* 2013).

These examples illustrate the complex basis of genetic determination of plasma TG concentrations. Growing evidence has led to a hypothesis that considers this newly emerging information from GWAS and the known phenotypic spectrum of HTG patients. This hypothesis suggests that elevated plasma TG concentrations are a result of an accumulation of deleterious alleles in genes associated with TG metabolism (Johansen and Hegele 2012a). On the opposite end of the spectrum, we find hypolipidemic cases with an accumulation of protective and/or lack of deleterious alleles in respective genes. Individuals with normal plasma TG levels represent an equilibrium between protective and deleterious alleles. Extremely elevated plasma TG levels (>10 mmol/l) are caused by the presence of loss-of-function mutations in both alleles of the respective gene (*LPL*, *APOC2*, *APOA5*, *LMF1*, and *GPIHBP1*), as discussed above. Phenotypic expression of polygenic HTG includes plasma TG concentration between 3.5-10 mmol/l, and this is the result of an accumulation of TG-elevating alleles of common functional variants in several genes (mostly *APOA5*, *GCKR*, *LPL*, *APOB*, *APOE*, *CREBH*, and *GPIHBP1*) (Johansen *et al.* 2010, Johansen and Hegele 2012a).

Modern high-throughput techniques for genetic and data analysis of large numbers of samples in a reasonable time (DNA arrays, NGS, GWAS approach) enable researchers to collect more data, most of which favors these hypotheses.

On the basis of these results, the Global Lipids Genetic Consortium (GLGC) has identified common variants in 32 genes (Table 1) that are strongly associated with HTG susceptibility, i.e. HTG-polygenic score (Johansen *et al.* 2011a, Johansen and Hegele 2011, 2012b). These variants also show a significant association with the typical variability seen in normotriglyceridemic subjects. Genetic risk score, assessed based on the presence of these TG-elevating alleles in an individual genome, was significantly higher in HTG patients compared to normal controls (Teslovich *et al.* 2010, Johansen *et al.* 2011b). The greater the number of these variants in the genome, the greater individual susceptibility to HTG development.

Conclusion

Recently, modern approaches such as genome wide association studies have identified multiple loci associated with plasma triglyceride levels. Additional research (mutation analysis by gene sequencing, animal models, and functional studies) has shown the important role these genes play in TG metabolic pathways. However, common and rare genetic variants only explain a small portion of the total variability (generally 10-20 %) associated with primary hypertriglyceridemia.

It is certain that future results of genetic studies carried out on large groups of normolipidemic and hyperlipidemic participants will contribute to the development of diagnostic algorithms for early identification of individuals at risk for gastrointestinal and cardiovascular complications. Such routine diagnostic procedures will be used to individualize preventive care and/or therapy in order to improve diagnostics, treatment, and prevention of the disease; this will subsequently decrease health care costs and lead to improved quality of life of affected individuals. The beneficiaries of this research will not only be the patients who will receive more considerate and efficient individualized care, but society as well, through reduced financial demands associated with this new form of individualized care.

Table 1. List of 32 loci associated with plasma TG concentrations, identified by GLGC, and genes involved in development of monogenic (mendelian) forms of HTG (modified from Johansen and Hegele 2012a).

	Locus	Chromosome	SNP/risk allele	Effect size mmol/l (mg/dl)
<i>Polygenic HTG (plasma TG concentration ~3.5-10 mmol/l)</i>	ANGPTL3	1	rs2131925/T	0.06 (4.94)
	GALNT2	1	rs1321257/G	0.03 (2.76)
	GCKR	2	rs1260326/T	0.10 (8.76)
	APOB	2	rs1042034/T	0.07 (5.99)
	COBLL1	2	rs10195252/T	0.02 (2.01)
	IRS1	2	rs2943645/T	0.02 (1.89)
	MSL2L1	3	rs645040/T	0.03 (2.22)
	KLHL8	4	rs442177/T	0.03 (2.25)
	TIMD4	5	rs1553318/C	0.03 (2.63)
	MAP3K1	5	rs9686661/T	0.03 (2.57)
	HLA	6	rs2247056/C	0.03 (2.99)
	MLXIPL	7	rs7811265/A	0.09 (7.91)
	TYW1B	7	rs13238203/C	0.09 (7.91)
	LPL	8	rs12678919 A	0.15 (13.64)
	TRIB1	8	rs2954029/A	0.06 (5.64)
	NAT2	8	rs1495743/G	0.03 (2.97)
	PINX1	8	rs11776767/C	0.02 (2.01)
	JMJD1C	10	rs10761731/A	0.03 (2.38)
	CYP26A1	10	rs2068888/G	0.03 (2.28)
	APOA5	11	rs964184/G	0.19 (16.95)
	FADS1-2-3	11	rs174546/T	0.04 (3.82)
	LRP1	12	rs11613352/C	0.03 (2.70)
	ZNF664	12	rs12310367/A	0.03 (2.42)
	LIPC	15	rs261342/G	0.03 (2.99)
	FRMD5	15	rs2929282/T	0.06 (5.13)
	CAPN3	15	rs2412710/A	0.08 (7.00)
	CETP	16	rs7205804/G	0.03 (2.88)
	CTF1	16	rs11649653/C	0.02 (2.13)
	APOE*	19	rs439401/C	0.06 (5.50)
	CILP2	19	rs10401969/T	0.09 (7.83)
	PLTP	20	rs4810479/T	0.04 (3.32)
	PLA2G6	22	rs5756931/T	0.02 (1.54)
			Number of described disease causing mutations (HGMD database)	
<i>Monogenic HTG (plasma TG concentration >10 mmol/l)</i>	LPL	8	179	
	GPIHBP1	8	19	
	APOA5	11	66	
	LMF1	16	11	
	APOC2	19	19	

SNP – single nukleotide polymorphism, HTG – hypertriglyceridemia, TG – triglyceride.

Conflict of Interest

There is no conflict of interest.

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