Genetics of Lipid and Lipoprotein Disorders and Traits

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Plasma lipids, namely cholesterol and triglyceride (TG), are carried within complex lipoprotein particles, such as lowdensity lipoprotein (LDL) and high-density lipoprotein(HDL) [1].

Lipids and lipoproteins serve numerous physiological roles.

the terms‘‘lipids’’& ‘‘lipoproteins’’ are often used interchangeably, especially by clinicians for convenience, they are different biochemical entities [1].

Plasma lipid levels represent the integrated lipid component of various lipoprotein species.

For instance,

plasma TG is the sum of TG carried within chylomicrons and very-low-density lipoprotein (VLDL) particles and their metabolic remnants, while plasma total cholesterol is the sum of cholesterol carried within these particles and also within LDL and HDL. In contrast, lipoproteins are discrete molecular entities that are likewise subject to manifold genetic and environmental influences and show complex metabolic interrelationships with one another [1].

Recent technological advances have helped identify numerous genetic variants, ranging from ultra-rare to common, which have significant effects, ranging from large to small, on inter-individual differences in plasma lipid and lipoprotein levels.

Over the past 3 years, the range of causative genes and mutations underlying rare familial dyslipidemia syndromes has expanded, while new insights have emerged from genotyping and next-generation sequencing (NGS) studies in unrelated individuals.

Genetic variation (GV)

genomic differences among individuals, that makes each or a group of organisms different from others. in which the number of copies of a particular segment

recent findings of

(1) rare genetic variants underlying monogenic dyslipidemias in clinically ascertained patients;

(2) common variants contributing to a polygenic component of clinical dyslipidemias;

(3) Common and rare variants contributing to variations of plasma lipids and lipoproteins in epidemiologic samples;

(4) common and rare variants from (3) that have been implicated as causative for atherosclerosis; and

(5) targets for drug development to treat dyslipidemia and possibly to prevent atherosclerosis.

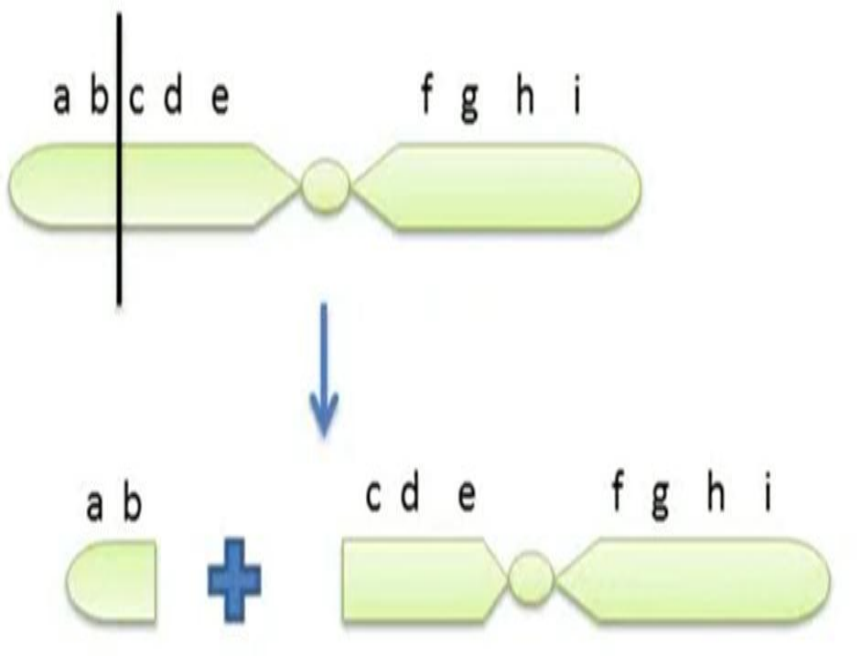
Expanding the Genetic Etiologies in Monogenic Dyslipidemias: Focus on Familial Hypercholesterolemia

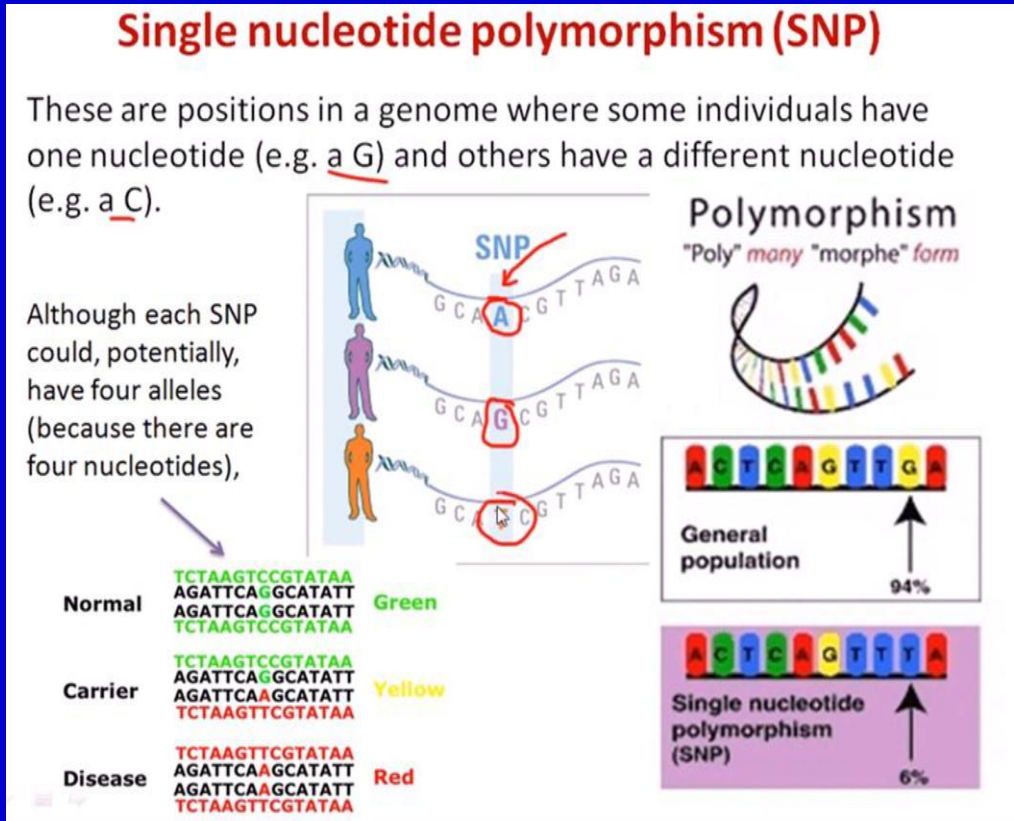
Monogenic dyslipidemias are classified according to the primary lipid or lipoprotein disturbance: elevated or depressed concentrations of LDL cholesterol (LDL-C) or HDL cholesterol (HDL-C), or elevated TG [1].

Currently, 27 monogenic dyslipidemias are defined by extreme deviations of plasma lipid or lipoprotein values typically with discrete clinical signs and symptoms caused by numerous rare mutations affecting a total of 25 genes (Table 1) [2].

other NGS efforts have identified a few rare large-effect variants in new genes underlying some of these disorders, particularly familial hypercholesterolemia (FH) [4]. FH mutation carriers show a relatively wide range of LDL-C levels;

Currently, nine genes underlie FH or FH-like phenotypes (Table 1). In addition to canonical causative genes, namely LDLR, APOB, and PSCK9 for co-dominant forms of FH, and LDLRAP1 (alias ARH) for purely recessive FH [8], NGS revealed that the APOE p.Leu167del variant causes a dominant presentation of FH [9, 10], while recessive mutations in ABCG5 (and likely ABCG8) [11] and LIPA can cause an FHlike phenotype [12].





Phenotype	Disorder	Alternative name	Gene symbol	Chr
High LDL-C	Familial hypercholesterolemia	Hyperlipoproteinemia type 2A	*LDLR*	19p13.3
	Familial defective apolipoprotein B	Autosomal dominant hypercholesterolemia type 2 (binding-defective apo B)	*APOB*	2p24-p23
	Autosomal dominant hypercholesterolemia	Autosomal dominant hypercholesterolemia type 3 (*PCSK9* gain-of-function)	*PCSK9*	1p32.3
	Autosomal dominant hypercholesterolemia	Autosomal dominant hypercholesterolemia type 4	*STAP1*	4q13.2
	Autosomal dominant hypercholesterolemia	Autosomal dominant hypercholesterolemia type 5	*APOE*	19q13
	Autosomal recessive hypercholesterolemia		*LDLRAP1 (ARH)*	1p36-p35
	Cholesterol ester storage disease	Includes Wolman disease	*LIPA*	10q21.31
	Sitosterolemia	Phytosterolemia	*ABCG5/ ABCG8*	2p21
Low LDL-C	Abetalipoproteinemia	Bassen-Kornzweig syndrome	*MTTP*	4q24
	Hypobetalipoproteinemia		*APOB*	2p24-p23
	PCSK9 deficiency with low LDL-C	Hypobetalipoproteinemia (*PCSK9* loss-of-function)	*PCSK9*	1p32.3
	Familial combined hypolipidemia	ANGPTL3 deficiency	*ANGPTL3*	1p31.1-p22.3
	Chylomicron retention disease	Anderson disease	*SAR1B*	5p31.1
High HDL-C	Cholesteryl ester transfer protein deficiency	Hyperalphalipoproteinemia	*CETP*	16q21
	Hepatic lipase deficiency		*LIPC*	15q21-q23
	Scavenger receptor B1 deficiency		*SCARB1*	12q23.31
	Endothelial lipase deficiency		*LIPG*	18q21.1
Low HDL-C	Tangier disease		*ABCA1*	9q31
	Apolipoprotein A-I deficiency		*APOA1*	11q23
	Familial LCAT deficiency (complete or partial)	Includes Fish-eye disease	*LCAT*	16q22
High TG	Lipoprotein lipase deficiency	Familial chylomicronemia	*LPL*	8p22
	Apolipoprotein C-II deficiency	Familial chylomicronemia	*APOC2*	19q13

Common and Low-Frequency Variants Associated with Lipid and Lipoprotein Traits

The Global Lipids Genetics Consortium (GLGC) genome wide association studies (GWASs) identified common genetic variants governing plasma lipids and lipoproteins in essentially normolipidemic populations [21, 22].

The157 loci identified by GLGC explain 10–20 % of the total variation in total, LDL-C, HDL-C, and TG, and a higher proportion of variation attributable to genetic factors [22].

Evaluating the polygenic determinants of plasma lipids typically starts with the lead SNP genotypes identified in these landmark publications [23]. Many of the genetic loci identified by GWAS—perhaps one-third—harbor genes whose products were already implicated in plasma lipoprotein metabolism [23]. Other associated loci have generated hypotheses to evaluate new pathways and mechanisms, as exemplified by molecular and biochemical studies of such GWAS specified genes as SORT1, TRIB1, and GCKR. Another new mechanistic lead was the association of lower total cholesterol and LDL-C levels with a SNP at the haptoglobin locus (HP) [21],

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Another new mechanistic lead was the association of lower total cholesterol and LDL-C levels with a SNP at the haptoglobin locus (HP) [21], which marks haplotypes with exonic deletions that likely affect expression of haptoglobin and possibly interaction with apolipoprotein (apo) E-containing lipoproteins [27].

Each new locus identified from GLGC could lead to comparable lines of investigation.

Association of Lipid and Lipoprotein Variants with Atherosclerotic Cardiovascular Disease

Many genetic determinants of plasma lipoproteins are also significant determinants of atherosclerotic CVD.

A recent synthesis of coronary heart disease (CHD) GWAS results indicated 58 significantly associated loci, of which about one-quarter overlapped with GWAS loci for lipids, outnumbering the contributions of loci associated with blood pressure or diabetes.

Because lipid-associated GWAS loci were determinants of either LDL-C, TG, or lipoprotein(a) (Lp[a]), the complexity of the biology seemed reducible to the common presence of apo B in these particles; genetic determinants of apo B-containing lipoproteins seemed to be the unifying element underlying these observations [30]. However, discordance between levels of apo B and LDL-C or TG is well-known [39]; furthermore, apo B and Lp(a) levels are uncorrelated. Until a GWAS of apo B (or non-HDL-C) concentration is performed, invoking apo B as the unifying intermediate phenotype for genetic determinants of CHD seems premature.

Genetic Evidence for a Causal role for LDL-C in Coronary Heart Disease Susceptibility

The causal relationship between LDL-C and CHD has been supported by early observations in families and cohorts with FH due to rare variants in LDLR [40]. More recently, an evaluation of 164 heterozygous carriers of 16 different rare gain-of-function variants in PCSK9 [41] showed a high prevalence of early onset CHD, with 33 % of carriers expressing symptoms and hard end-points at mean age of 49 years.

Renaissance of Lipoprotein(a)

The relationship between Lp(a) and atherosclerosis has been appreciated for decades [80]. Recent meta-analyses using SNPs at LPA locus onchromosome 6q25-26 confirm association with CHD. GWAS also shows that LPA genotype is significantly associated with CHD. The range of associated phenotypes has recently been broadened to include calcific aortic stenosis and heart failure. This convergence of genetic data suggesting that isolated reduction of Lp(a) can protect against CHD and other adverse phenotypes has prompted development of antisense therapy targeting Lp(a), This agent should help advance evaluation of Lp(a)'s role in pathogenesis and of possible benefits of targeted reduction. It is also interesting that PCSK9 monoclonal antibodies reduce plasma Lp(a) levels by *30 % [87], which may explain part of their clinical benefits [88].

Translation to Other Therapies

PCSK9 inhibitors, whose development could be traced to human genetic observations, are now in widespread clinical use& appear to have beneficial effects on outcomes, as well as potential adverse effects & economic implications. Analogous advances include development of an anti-sense inhibitor of APOC3 (volanesorsen) as a treatment for familial chylomicronemia due to homozygous mutations in LPL& other genetically undefined forms of severe hypertriglyceridemia. While volanesorsen may prove to be useful clinically for severe hypertriglyceridemia with its attendant risk of life-threatening pancreatitis, suggestions that it might also be used to prevent CHD need to be carefully considered. The specific targeting of APOC3 has pleiotropic effects on the lipid profile, including reductions of apo C-III-containing subfractions of LDL, HDL, and Lp(a). Also, ANGPTL3 and ANGPTL4 are active drug targets as they modulate LPL activity, and because of the apparently favorable phenotypes observed in carriers of inactivating or loss-of-function variants.