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Dyslipidemia: Genetics and Role in the Metabolic Syndrome

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1. Introduction

Dyslipidemia is characterized by an aggregation of lipoprotein abnormalities including low high density lipoprotein cholesterol (HDL-C), high serum triglycerides (TG) and increased small low density lipoprotein cholesterol (LDL-C). Lipoproteins, which contain lipids and proteins (apolipoproteins, APO) are responsible, primarily, for transporting water insoluble lipids (cholesterol, TG) in plasma from the intestines and liver, where they are absorbed and synthesized, respectively, to peripheral tissues (muscle, adipose) for utilization, processing and/or storage (Kwan et al., 2007). There are several subtypes of lipoproteins with specific functions including, from smallest to largest: 1) chylomicrons, which transport dietary TG from the intestines to the peripheral tissue and liver; 2) very LDL (VLDL) particles, which transport TG from the liver to peripheral tissues; 3) intermediate density lipoproteins (IDL), which are produced from VLDL particle metabolism and may be taken up by the liver or further hydrolyzed to LDL; and, 4) HDL, which is key in 'reverse cholesterol transport' or shuttling cholesterol from peripheral cells to the liver (Kwan et al., 2007).

The Metabolic Syndrome (MetSyn) is a clustering of traits including dyslipidemia as well as hypertension (raised systolic and/or diastolic blood pressure), dysglycemia (high fasting glucose) and obesity (high body mass index (BMI) and/or waist circumference). Dyslipidemia is formally defined within the context of MetSyn. Various diagnostic definitions have been proposed for MetSyn by several organizations including the World Health Organization (WHO) (Alberti and Zimmet, 1998), European Group Insulin Resistance (EGIR) (Balkau and Charles, 1999), National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III, (2001), International Diabetes Federation (IDF, (Alberti et al., 2005), American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) (Grundy et al., 2006) and, with the most recent joint interim statement proposed by the AHA/NHLBI, IDF and other organizations (Alberti et al., 2009). Although the recommendations differ widely on the obesity component, the dyslipidemia component has been fairly consistently defined as having TG ≥ 150 mg/l, HDL-C <40 mg/dL (1.03 mmol/l, in males) or <50 mg/dL (1.29 mmol/l in females) or drug treatment for elevated TG or low HDL-C (NCEP ATP III: (2001), IDF: (Alberti et al., 2005), Joint Statement: (Alberti et al., 2009)). However, the WHO (Alberti and Zimmet, 1998) proposed slightly lower limits for HDL-C (male: < 0.9 mmol/l (35 mg/dl); female: < 1.0 mmol/l (39 mg/dl)) and the EGIR (Balkau and Charles, 1999) recommended dyslipidemia be defined by HDL-C < 1.0 mmol/l (39 mg/dl) or TG > 2.0 mmol/l (177 mg/dl). There is currently no recommended value for

LDL-C levels in the context of MetSyn yet LDL-C remains the primary target of therapy for the management of high blood cholesterol per the most recent guidelines from the NCEP ATPIII, which recommended drug therapy for LDL-C values ranging from ≥100 mg/dl to ≥190 mg/dl depending on the presence/absence of other coronary heart disease (CHD) risk factors (Grundy et al., 2004). When LDL becomes lipid depleted, small dense LDL (sdLDL) particles are formed, which have a lower affinity for the LDL receptor (LDLR), more susceptibility to oxidation and a higher affinity for macrophages; and, thus, sdLDL particles contribute to the atherosclerotic process (Austin et al., 1990; Littlewood and Bennett, 2003) and likely MetSyn (Kruit et al., 2010).

Dyslipidemia and MetSyn are common in developed nations and the prevalence of both are rising worldwide, which may be attributed, in part, to the rising rates of overweight and obesity (Alberti et al., 2009; Halpern et al., 2010). According to the National Health and Nutrition Examination Survey (NHANES) III (1988-1994) in the United States (U.S.), which used the NCEP ATP III criteria, the age-adjusted prevalence of dyslipidemia defined by high TG or low HDL-C, was approximately 30.0% and 37.1%, respectively; and, the prevalence of MetSyn was approximately 23.7% (Ford et al., 2002). The prevalence of dyslipidemia and MetSyn generally increase with increasing age (Ford et al., 2002). However, in a more recent study that used the Health Survey for England (HSE) (2003-2006) survey data and NHANES (1999-2006) data with exclusion of persons over 80 years old, the prevalence of low HDL-C (defined in both males and females as <40 mg/dL) was 10.0% in England and 19.2% in the U.S. (Martinson et al., 2010). Thus, the prevalence can vary markedly depending on how these traits are defined (Cook et al., 2008). Interestingly, trends in the U.S. and England indicate during the past two decades an increase in the proportion of individuals diagnosed with high cholesterol (≥240 mg/dL) but who achieved therapeutic control (Roth et al., 2010). For example, in the U.S. in 2006, 54.0% of men (95% CI: 47.6–60.4) and 49.7% of women (95% CI: 44.3–55.0) with high total serum cholesterol were on cholesterol-lowering medication, as opposed to 10.8% of men (95% CI: 8.0–13.6) and 8.6% (95% CI: 6.7–10.6) of women in 1993 (Roth et al., 2010). In England, in 2006, 35.5% of men (95% CI: 32.8–38.3) and 25.7% of women (95% CI: 23.4–28.1) were on cholesterol-lowering medication as opposed to 0.6% of men (95% CI: 0.3–1.3) and 0.4% of women (95% CI: 0.1–0.7%) in 1993 (Roth et al., 2010). Thus, prevalence rates will also vary by whether or not relevant drug treatments have been considered and, perhaps, the list of relevant drugs should include cholesterol lowering therapies (e.g., statins) as well as other drugs (e.g., tamoxifen, glucocorticoids) known to alter TG and cholesterol levels (Garg and Simha, 2007).

Both dyslipidemia and MetSyn increase the risk of Type II diabetes mellitus (T2DM) (Adiels et al., 2006; Kruit et al., 2010) and cardiovascular disease (CVD) morbidity (Alberti et al., 2009; Linsel-Nitschke and Tall, 2005) and CVD mortality (Lewington et al., 2007). Patients with MetSyn have a five-fold increase in the risk of developing T2DM and are at twice the risk of developing CVD over the next 5 to 10 years compared to individuals without the syndrome (Alberti et al., 2009). In the presence of both MetSyn and T2DM, the prevalence of CVD is markedly increased with an odds ratio (OR) of 3.04 [95% confidence interval (CI) of OR: 1.98-4.11] in comparison to those with none of these conditions (Athyros et al., 2004). The importance of MetSyn is exemplified by its ICD-9 code (277.7), which was initially established as a diagnosis of "Dysmetabolic Syndrome X" (Einhorn et al., 2003; Kahn et al., 2005). In summary, both dyslipidemia and MetSyn are substantial public health problems, which require a better understanding of their respective etiologies to develop more effective lifestyle and therapeutic interventions.

Heritability estimates suggest there is a strong genetic component to dyslipidemia and MetSyn. Heritability estimates for dyslipidemia range from 0.20 to 0.60 (Edwards et al., 1997; Goode et al., 2007; Herbeth et al., 2010; Kronenberg et al., 2002; Wang and Paigen, 2005) and from 0.24 to 0.63 for MetSyn (Lin et al., 2005; Sung et al., 2009).

Multiple genetic variants in the form of single nucleotide polymorphisms (SNPs) (i.e., single DNA base changes) have been associated with manifestation of dyslipidemia and MetSyn. In this chapter, we review and summarize associations between common SNPs (i.e., those with a minor allele frequency (MAF) ≥0.05) in the most biologically plausible candidate genes and HDL-C, LDL-C and TG levels as well as MetSyn as a single, unifying trait. Previous estimates suggest all common variants together explain less than 10 percent of HDL-C levels in the general population (Kronenberg et al., 2002); however, more elegant statistical modeling methods that combine SNPs in a more biologically meaningful way may be needed to better understand the collective role of genetic variants in manifestation of dyslipidemia, MetSyn and other complex metabolic traits. As a result, at the end of this chapter, we review studies that have undertaken more complex modeling strategies to understand the aggregate effects of SNPs in manifestation of dyslipidemia and MetSyn and provide our insights for future directions in this field.

2. Genetic variants in lipid metabolism and HDL-C levels

As mentioned above, HDL-C is important for "reverse cholesterol transport" or the shuttling of cholesterol from peripheral cells to the liver. Many of the genetic variants associated with HDL-C levels have been summarized nicely in a recent comprehensive review by Boes et al. (Boes et al., 2009). In Table 1, we include common SNPs tabulated in Boes et al. (2009) review of large studies (ethnic group sample sizes ≥500) as well as common SNPs in large studies that have been identified since their review.

Gene	Polym.	rs Number	MAF	Ethn.	Sample Size	Results (Effect Size, p-value)	Reference
ABCA1	C (-297)T	rs2246298	0.25 (T)	A	1625 (GP)	p=0.0455	(Shioji et al. 2004b)
ABCA1	G (-273)C	rs1800976	0.40 (C)	A	1626 (GP) 735 (HBP)	+1.9/+2.7 mg/dl (1/2copies); p=0.03 +1.9 /+5.0 mg/dl (1/2 copies); p=0.03	(Shioji et al. 2004b)
ABCA1	G (-273)C	rs1800976	0.38 (T)	Tu	2332 (GP)	+0.7/+1.9 mg/dl (1/2 copies); p<0.02	(Hodoglugil et al. 2005)
ABCA1	G378C	rs1800978	0.13 (C)	W	5040 (GP)	-1.2/- 2.7 mg/dl (1/2 copies); p=0.03	(Porchay et al. 2006)
ABCA1		rs3890182	0.13 (A)	W	5287 (GP)	-1/-3 mg/dl (1/2 copies) ; p=0.003	(Kathiresan et al. 2008)
ABCA1		rs2275542		A	<1880 (GP)	p=0.006	(Shioji et al. 2004b)

ABCA1		rs2515602	0.27	B	1943 (P)	M; p=0.034; F; p<0.001	(Klos et al. 2006a)
ABCA1	G596A	rs2853578	0.28 (A)	W	2468 CVD 834 (Co)	0.2 /+2.8 mg/dl (1/2 copies); p=0.02	(Whiting et al. 2005)
ABCA1	2310G>A	rs2066718	0.03 (A)	W	9123 (P)	F: higher levels in carriers; p=0.02	(Frikke-Schmidt et al. 2004)
ABCA1	G2706A	rs2066718	0.05 (A)	Tu	2458 (GP)	M: +2.0 mg/dl for heterozygotes; p<0.01	(Hodoglugil et al. 2005)
ABCA1	2472G>A G2868A	rs2066718	0.06 (A)	Tu	2105 (GP)	F: +3.1 mg/dl for carriers; p=0.0005	(Hodoglugil et al. 2005)
ABCA1	1883M	rs4149313	0.12 (G)	W	9123 (P)	F: + heterozygotes; p=0.05	(Frikke-Schmidt et al. 2004)
ABCA1	32b.+30, ABC32			W	1543 (P)	-2.2 mg/dl for carriers ; p=0.0040	(Costanza et al. 2005)
ABCA1	R1587K	rs2230808	0.24 (A)	W	9123 (P)	M: - 1.5 mg/dl for heterozygotes; p=0.008	(Frikke-Schmidt et al. 2004)
ABCA1	4759G > A	rs2230808	0.26 (K)	W	779 (CVD)	-1.5 mg/dl for carriers; p=0.03	(Clee et al. 2001)
ABCA1	50b.3038, ABC50	rs41474449	.	W	1543 (P)	+1.6 mg/dl for carriers; p=0.043	(Costanza et al. 2005)
ABCA1		rs3890182	0.12 (A)	EA	25,167	p= 4.53E-07	(Dumitrescu et al. 2011)
APOA1	T84C (HaeIII)	rs5070	0.23 (C)	A	1637 (GP)	+1.9 /+5.4 mg/dl (1/2copies); p=0.0005	(Shioji et al. 2004a)
APOA1	MspI RFLP	rs5069	0.31 (C)	B	3831 (P)	M/F; p=n.s/0.022	(Brown et al. 2006)
APOA1		rs28927680	0.93 (G)	EA	25,167	p= 8.61E-09	(Dumitrescu et al. 2011)
APOA1		rs964184	0.86 (C)	EA	25,167	p= 6.08E-10	(Dumitrescu et al. 2011)
APOA5	- 1131T > C	rs662799	0.06 (C)	UK	1696 (P)	-1.5 mg/dl /-5.4 mg/dl (1/2 copies) ; p=0.04	(Talmud et al. 2002a)
APOA5	- 1131T > C	rs662799	0.07 (C)	W	1596(SAPHIR)	-3.5 mg/dl per copy; p=0.00038	(Grallert et al. 2007)
APOA5	- 1131T > C	rs662799	0.23–0.30 (C)	C, Ma	2711 (C) 707 (M)	-2.3/- 5.4 mg/dl 1/2 copies; p<0.0001 - 1.2 /- 8.1 mg/dl 1/2 copies; p<0.0001	(Lai et al. 2003)

APOA5	- 1131T > C	rs662799	0.34 (C)	A	521 HoCo	-3.3 mg/dl per copy; p<0.001	(Yamada et al. 2007)
APOA5	-3A > G	rs651821	0.07	W	2056 (P)	M; p=0.30; F; p=0.26	(Klos et al. 2006a)
APOA5	-3A > G	rs651821	0.18 (G)	C	2711 (GP)	-2.3/-5.8 mg/dl 1/2 copies ; p<0.0001	(Lai et al. 2003)
APOA5	-3A > G	rs651821	0.34 (C)	A	5207 (Ho Co, P)	-2.7 mg/dl per copy; p<0.001	(Yamada et al. 2007)
APOA5	-3A > G	rs651821	0.36 (G)	A	2417 (Ho Co)	-3.9 /- 7.0 mg/dl 1/2 copies ; p<0.001	(Yamada et al. 2008)
APOA5	S19W	rs3135506	0.06 (W)	UK	1660 (P)	-1.9 /+1.2 mg/dl (1/2 copies); p=0.02	(Talmud et al. 2002a)
APOA5	56C>G	rs3135506	0.06 (G)	W	2347 (P)	-2.0 mg/dl for carriers; p=0.008	(Lai et al. 2004)
APOA5		rs2072560	0.16 (A)	C	2711 (GP)	-1.9 /-3.9 mg/dl (1/2 copies) ; p=0.003	(Lai et al. 2003)
APOA5	IVS3+476 G>A	rs2072560		Ma	707 (P)	-0.4 /9.3 mg/dl (1/2 copies) ; p=0.004	(Qi et al. 2007)
APOA5	V153M	rs3135507		W	2557	F:- 3.5 mg/dl for carriers; p<0.01	(Hubacek 2005)
APOA5	+553	rs2075291	0.07 (T)	A	5206 HoCo	-4.6 mg/dl per copy; p<0.001	(Yamada et al. 2007)
APOA5	Gly185Cys	rs2075291	0.08 (T)	A	2417 HoCo	-5.0 /-11.2 mg/dl (1/2 copies); p<0.001	(Yamada et al. 2008)
APOA5	1259T>C	rs2266788	0.18 (C)	C	2711 (GP)	-2.3 /-3.1 mg/dl 1/2 copies; p<0.0001	(Lai et al. 2003)
APOB		rs11902417	0.78 (G)	E	17723	p= $3.7x10^{-7}$	(Waterworth et al. 2010)
APOC3	C455T	rs2854116	0.41 (C)	In	1308 (P)	-3.1/-5.4 mg/dl (1/2 copies) ; p<0.05	(Lahiry et al. 2007)
APOC3	PvuII	rs618354	0.49	A	F:291 (GP)	F: +0.1/-4.2 mg/dl 1/2 copies;p=0.029	(Kamboh et al. 1999)
APOC3	Sst1 RFLP	rs5128	0.09 (S2)	W	M:1219 (P)	M: -1.8 mg/dl for carriers; p=0.04.	(Russo et al. 2001)
APOC3	3′-utr/Sac I	rs5128	0.09 (+)	Hu	713 (P)	-5.0 mg/dl for heteroz.; p=0.0014	(Hegele et al. 1995)

APOC3	3238C > G	rs5128	0.07 (S2)	W	906 (GP)	+1.9 mg/dl for carriers; p=0.079	(Corella et al. 2002)
APOE	Cys112Arg	rs429358	0.16 (A)	N	3575	p=0.001	(Povel et al. 2011)
CETP	G2708A	rs12149545	0.30 (A)	W	2683 GP 556 Cvd	+1.9 mg/dl per copy; p<0.001	(McCaskie et al. 2007)
CETP	G2708A	rs12149545	0.31 (A)	W	709 (CVD)	+1.5 /+3.5 mg/dl (1/2 copies) ;p=0.0016	(Klerkx et al. 2003)
CETP		rs3764261	0.14 (T)	C	4192	+0.07 mg/dl; $p=4.3x10^{-14}$	(Liu et al. 2011)
CETP	G971A	rs4783961	0.49 (A)	W	709 (CVD)	+1.2/+1.9 mg/dl (1/2 copies) ; p=0.09	(Klerkx et al. 2003)
CETP	C629A	rs1800775	0.48 (A)	W	7083 (P)	+2.7 /+5.4 mg/dl (1/2 copies); p<0.001	(Borggreve et al. 2005a)
CETP	C629A	rs1800775	0.51 (A)	W	847 M, 873 F (P)	+4.2 mg/dl for homoz.; p<0.002	(Bernstein et al. 2003)
CETP	C629A	rs1800775	0.49 (A)	W	5287 (GP)	+3 /+5 mg/dl (1/2 copies) ; p= 2x10-29	(Kathiresan et al. 2008)
CETP	C629A	rs1800775	0.42 A	A	4050 (GP)	+2.2/+3.4 mg/dl 1/2 copies; p=3.28x10-9	(Tai et al. 2003b)
CETP	C629A	rs1800775	0.48 (A)	W	2683 GP 556 Cvd	+2.7 mg/dl per copy; p<0.001	(McCaskie et al. 2007)
CETP	C629A	rs1800775	0.40 (A)	W	1214 (CVD) 574 (Co)	CVD: +2.0/3.5mg/dl (1/2 copies) ; p=0.02 Co: +3.3/6.1 mg/dl (1/2 copies) ; p=0.05	(Blankenberg et al. 2004)
CETP	C629A	rs1800775	0.44 (A)	W	709 (CVD)	+0.8/3.9 mg/dl (1/2 copies) ; p<0.0001	(Klerkx et al. 2003)
CETP	C629A	rs1800775	0.50 (A)	W	309 (MI) 757 (Co)	+1.9/6.1 mg/dl (1/2 copies) ; p<0.0001	(Eiriksdottir et al. 2001)
CETP	C629A	rs1800775	0.48 (A)	W	498 (cvd) 1107(Co)	+2.9/4.4 mg/dl (1/2 copies) ; p<0.001	(Freeman et al. 2003)
CETP	Taq1B	rs708272	0.40 (B2)		13,677 (Meta)	+1.2 /+3.8 mg/dl 1/2 copies; p<0.0001	(Boekholdt et al. 2005)

CETP	Taq1B	rs708272			>10,000 (Meta)	+4.6 mg/dl for homoz.; p<0.00001	(Boekholdt & Thompson 2003)
CETP	Taq1B	rs708272	0.42 (B2)	W	7083 (P)	+2.7/5.0 mg/dl (1/2 copies) ; p<0.001	(Borggreve et al. 2005b)
CETP	Taq1B	rs708272	0.44 (B2)	W	2916 (P)	+2.5/4.7 mg/dl (1/2 copies) ; p<0.001	(Ordovas et al. 2000)
CETP	Taq1B	rs708272	0.43 0.26 (A)	W B	2056 1943 (P)	p<0.01; p<0.02	(Klos et al. 2006b)
CETP	Taq1B	rs708272	0.44 0.27 (A)	W B	8764 (P)	+2.3/5.8 mg/dl (1/2 copies) ; p<0.001 +3.8/9.8 mg/dl (1/2 copies) ; p<0.001	(Nettleton et al. 2007)
CETP	Taq1B	rs708272	0.41 (A)	W	1503 (P)	+2 /+5 mg/dl (1/2 copies) ; p<0.001	(Sandhofer et al. 2008)
CETP	Taq1B	rs708272	0.33 (A)	A	4207 (GP)	+2.5/4.4 mg/dl (1/2 copies ; p=1.25x10-10	(Tai et al. 2003b)
CETP	Taq1B	rs708272	0.40 (A)	A	1729 (GP)	M: +1.2/3.5 mg/dl (1/2 copies); p=0.096 F: +1.9/6.2 mg/dl (1/2 copies); p<0.001	(Tsujita et al. 2007)
CETP	Taq1B	rs708272	0.42 (A)	W	2683 GP 556 CVd	+2.7 mg/dl per copy; p<0.001	(McCaskie et al. 2007)
CETP	Taq1B	rs708272	0.42 (A)	W	2392 cvd 827 Co	+1.7/3.6 mg/dl (1/2 copies) ; p<0.001	(Whiting et al. 2005)
CETP	Taq1B	rs708272	0.40 (A)	W	1464 CVD	+2.1/3.0 mg/dl (1/2 copies) ; p=0.003	(Carlquist & Anderson 2007)
CETP	Taq1B	rs708272	0.41 (A)	W	1200 CV 571 (Co)	+2.6 /+4.3 mg/dl (1/2 copies) ; p<0.02	(Blankenberg et al. 2004)
CETP	Taq1B	rs708272	0.44 (A)	W	499 CVD 1105 Co	+2.1/3.6 mg/dl (1/2 copies) ; p<0.001	(Freeman et al. 2003)
CETP	+784CCC	rs34145065	0.39 (A)	W	709 (CVD)	+1.2/3.5 mg/dl (1/2 copies) ; p=0.0009	(Klerkx et al. 2003)

CETP	A373P	rs5880	0.05 (A)	W	8467 P 1636 CV	5.4 mg/dl for heteroz.; p<0.0001	(Agerholm-Larsen et al. 2000)
CETP	Ile405Val	rs5882			>10,000 (Meta)	+1.9 mg/dl for homoz. ; p<0.00001	(Boekholdt & Thompson 2003)
CETP	A + 16G/Ex.14	rs61212082	0.32 (A)	W	6421 (P)	M: +1.5/2.3 mg/dl (1/2 copies); p=0.002 F: +0.0/+2.3 mg/dl (1/2 copies); p=0.007	(Isaacs et al. 2007)
CETP		rs61212082	0.30 (A)	W	1208 (CVD) 572 (Co)	+1.4 /+3.1 mg/dl (1/2 copies) ; p=0.08 +0.3 /+8.4 mg/dl (1/2 copies); p=0.003	(Blankenberg et al. 2004)
CETP		rs61212082	0.30 (A)	W	498 (CVD) 1108 (Co)	+1.2 /+3.5 mg/dl (1/2 copies); p<0.05 +1.5 /+1.5 mg/dl (1/2 copies); p<0.05	(Freeman et al. 2003)
CETP	D442G	rs2303790b	0.03 (A)	A	3469 (He Ex)	+4.9 mg/dl for heteroz.; p<0.001	(Zhong et al. 1996)
CETP	R451Q	rs1800777	0.04 (A)	W	8467 (P) 1636 (CVD)	5.4 mg/dl for heterozygotes ; p<0.001	(Agerholm-Larsen et al. 2000)
CETP	G + 82A/Ex15	rs1800777	0.03 (A)	W	1071 CV 532 Co	3.6 /5.2 mg/dl for heteroz.; p=0.06/0.07	(Blankenberg et al. 2004)
CETP		rs12596776	0.90 (C)	EA	25,167	p=1.18E-05	(Dumitrescu et al. 2011)
CETP		rs9989419	0.39 (A)	EA	25,167	p=1.71E-53	(Dumitrescu et al. 2011)
LCAT	Gly230Arg			W	156 low 160 high	Variant sig. only in low HDL group	(Miettinen et al. 1998)
LCAT	608C/T	rs5922	.	A	203 (CVD)	Increase in HDL; p=0.015	(Zhang et al. 2003)
LCAT		rs5922		A	150 Str 122 Co	Lower HDL-C in heteroz.; p<0.05	(Zhu et al. 2006)
LCAT	P143L +511C>T			A	190 CVD 209 (Co)	Association with low HDLC; p<0.01	(Zhang et al. 2004)
LCAT		rs2292318	0.12 (A)	W	1442 CVD,Co	Increases HDLC; p=2 x 10 -5	(Pare et al. 2007)

LDLR	Exon 2	rs2228671		W	1543 (P)	+3.8 mg/dl for carriers; p=0.0056	(Costanza et al. 2005)
LDLR	1866C > T Asn591Asn	rs688 = rs57911429	0.12 (T)	A	2417 (Ho Co)	+1.5 /+8.5 mg/dl (1/2 copies) ; p=0.0155	(Yamada et al. 2008)
LDLR	Exon 12/HincII	rs688 = rs57911429	0.39 (+)	Hu	713 (P)	2.3 / 4.3 mg/dl (1/2 copies) ; p=0.047	(Hegele et al. 1995)
LDLR	2052T >C	rs5925 = rs57369606	0.17 (C)	A	2417 HoCo	+1.2/+5.4 (1/2 copies) ; p=0.043	(Yamada et al. 2008)
LIPC	T-710C	rs1077834	0.22 (C)	W	9121 (P)	+3–4% per copy; p<0.001	(Andersen et al. 2003)
LIPC	C-514Ta	rs1800588	0.25 (T)	Va	>24,000 (Meta)	+1.5 /+3.5 mg/dl (1/2 copies); p<0.001	(Isaacs et al. 2004)
LIPC	Pos.-480T	rs1800588	0.21 (T) 0.53 (T)	W B	8897 (P) 2909 (P)	W: +2.2/+3.8 mg/dl (1/2 copies); p<0.001 B: +1.6/+4.0 mg/dl (1/2 copies); p<0.001	(Nettleton et al. 2007)
LIPC		rs1800588	0.21 (T)	W	6239 (P)	+1.3/+4.3 mg/dl (1/2 copies); p<0.001	(Isaacs et al. 2007)
LIPC		rs1800588	0.38 (T)	A	2170 (P)	+2.3 /+2.7 mg/dl (1/2 copies); p=0.001	(Tai et al. 2003a)
LIPC		rs1800588	0.21 (T)	W	5287 (GP)	+1 /+4 mg/dl (1/2 copies) ; p=4x 10 -10	(Kathiresan et al. 2008)
LIPC		rs1800588	0.25 (T)	W	2773 (GP)	+1.5 mg/dl per copy; p=0.04	(Talmud et al. 2002b)
LIPC		rs1800588	0.24 (T)	W	3319 CV 1385 Co	+1.0 /+3.8 mg/dl (1/2 copies); p=0.001	(Whiting et al. 2005)
LIPC		rs1800588	0.51 (T)	A	5207 Ho Co	+2.5 mg/dl per copy; p<0.001	(Yamada et al. 2007)
LIPC		rs1800588	0.21 (T)	W	6412 (CVD)	+2.0–2.5 mg/dl per copy; p<0.001	(McCaskie et al. 2006)
LIPC	G -250A	rs2070895	0.22 (A)	W	9121 (P)	+3–4% per copy; p<0.001	(Andersen et al. 2003)
LIPC		rs2070895		W	1543 (P)	+1.5 mg/dl for carriers; p=0.020	(Costanza et al. 2005)
LIPC		rs2070895	0.32 (A)	W	514 (P)	M; p=0.001	(de Andrade et al. 2004)

LIPC		rs2070895	0.23 (A)	W	5585 (P)	+3.9/3.9 mg/dl (1/2 copies); p=8x10-10	(Grarup et al. 2008)
LIPC		rs2070895	0.51 (A)	A	5213 HoCo	+2.7 mg/dl per copy; p<0.001	(Yamada et al. 2007)
LIPC		rs2070895	0.39 (A)	A	716 HeEx	+2.1 mg/dl for carriers; p=0.026	(Ko et al. 2004)
LIPC		rs12594375	0.37 (A)	A	2970 (GP)	p=0.00003	(Iijima et al. 2008)
LIPC		rs8023503	0.38 (T)	A	2970 (GP)	p=0.0001	(Iijima et al. 2008)
LIPC	+1075C	rs3829462	0.05 (C)	A	823	+8.0 mg/dl for heterozygotes; p<0.05	(Fang & Liu 2002)
LIPC		rs4775041	0.29C	EA	25,167	p=1.03E-16	(Dumitrescu et al. 2011)
LIPC		rs261332	0.20 (A)	EA	25,167	p=1.99E-13	(Dumitrescu et al. 2011)
LPC		rs261334	0.20 (T)	E	17723	p= 4.9×10^{-22}	(Waterworth et al. 2010)
LIPG	-384A > C	rs3813082	0.12 (C)	A	541 (Co)	+1.3/+10.2 mg/dl (1/2 copies) ; p=0.021	(Hutter et al. 2006)
LIPG		rs3813082	0.12 (C)	A	340 (Kids)	+0.7/+9.8 (1/2 copies) ; p=0.0086	(Yamakawa-Kobayashi et al. 2003)
LIPG	584 C/T T111l	rs2000813	0.32 (I)	W	495 (GP)	M: 1.2 /+2.7 mg/dl (1/2 copies) ; p=0.82 F: 0.4 /+1.9 mg/dl (1/2 copies) ; p=0.09	(Paradis et al. 2003)
LIPG		rs2000813	0.24 (T)	A	541 (Co)	+0.5/+6.1 mg/dl (1/2 copies) ; p=0.048	(Hutter et al. 2006)
LIPG		rs2000813	0.30 (T)	A	265 CVD 265 Co	+3.7 for carries; p=<0.02	(Tang et al. 2008)
LIPG		rs2000813	0.29 (T)	W 90%	372 (CVD)	+1.6 /+6.0 mg/dl (1/2 copies) ; p=0.035	(Ma et al. 2003)
LIPG	C+42T/ln 5	rs2276269	0.44 (T)	W	594 (HDL)	Decreases HDLC; p=0.007	(Mank-Seymour et al. 2004)

LIPG	T+2864C/In8	rs6507931	0.42 (C)	W	594 (HDL)	Decreases HDLC; p=0.004	(Mank-Seymour et al. 2004)
LIPG	2237G > A	rs3744841	0.36 (A)	A	340 (Kids)	4.0 mg/dl /-4.3 mg/dl (1/2 copies) ; p=0.011	(Yamakawa-Kobayashi et al. 2003)
LPL	D9N; Asp9Asn	rs1801177		–	5067 (Meta)	-3.1 mg/dl for heteroz.; p=0.002	(Wittrup et al. 1999)
LPL	Gly188Glu			–	10,434 (Meta)	- 9.7 mg/dl for heteroz.; p<0.001	(Wittrup et al. 1999)
LPL	N291S	rs268		–	14,912 (Meta)	-4.6 mg/dl for heteroz.; p<0.001	(Wittrup et al. 1999)
LPL	HindIII; Int8	rs320	0.30 (H)	W	520 (P)	+5.5 mg/dl in H – H- vs. H+H+; p=0.025	(Senti et al. 2001)
LPL	HindIII; Int8	rs320	0.26 (H1)	W	1361 (P)	M: +3.5 mg/dl for heteroz. ; p=0.0018 F : +4.2 mg/dl for heteroz. ; p=0.0212	(Holmer et al. 2000)
LPL	HindIII; Int8	rs320	0.32 (H)	W	906 (GP)	+1.9 mg/dl; p=0.003	(Corella et al. 2002)
LPL	HindIII; Int8	rs320		A	550 (NGT) 465 (DM)	NGT: +3.0 mg/dl for carriers; p<0.05 DM: +1.0 mg/dl for carriers; p<0.05	(Radha et al. 2006)
LPL	HindIII; Int8	rs320	0.27-0.31	NHW, H	615(W); 579(H)	p=0.005	(Ahn et al. 1993)
LPL		rs326	0.44	B	1943 (P)	M; p=0.013; F; p=0.004	(Klos et al. 2006a)
LPL	S447X Ser447Ter	rs328			4388 (Meta)	+1.5 mg/dl for heteroz.; p<0.001	(Wittrup et al. 1999)
LPL	S447X Ser447Ter	rs328	0.10 (G)	W	8968 (P)	+2.8 /+4.0 mg/dl (1/2 copies); p<0.001	(Nettleton et al. 2007)
LPL	S447X Ser447Ter	rs328	0.07 (G)	B	2677 (P)	+3.1 /+12.6 mg/dl (1/2 copies); p<0.001	
LPL	S447X	rs328	0.11 (X)	A	4058 (P)	+3.1 mg/dl; p<0.001	(Lee et al. 2004)
LPL		rs328		W	1543 (P)	+2.7 mg/dl; p=0.0017	(Costanza et al. 2005)
LPL		rs328			25,167	P=5.6E-22	(Dumitrescu et al. 2011)
LPL		rs328	0.09 (G)	W	5287 (GP)	+3 /+5 mg/dl (1/2 copies); p=3 x 10-12	(Kathiresan et al. 2008)

LPL		rs325	0.89 (T)	E	17723	p= 7.8×10-25	(Waterworth et al. 2010)
MLXIPL		rs17145738	0.12 (T)	EA	25,167	p=1.64E-05	(Dumitrescu et al. 2011)
PON1	Q192R	rs662 = rs60480675	0.30 (G)	W	1232 (P)	W: +0.1 /+2.3 mg/dl (1/2 copies) ; p=0.041	(Srinivasan et al. 2004)
PON1	Gln192Arg	rs662 = rs60480675	0.67	B	554	-5.4 /- 6.7 mg/dl (1/2 copies) ; p=0.008	"
PON1		rs662 = rs60480675	0.29 (R)	Hu	738 (P)	-3.1 mg/dl /- 3.1 mg/dl (1/2 copies) ; p=0.001	(Hegele et al. 1995)
PON1		rs662 = rs60480675	0.36 (R)	W-Bra	261 CVD, Co	M: +1.5 /+2.7 mg/dl (1/2 copies) ; p=0.035	(Rios et al. 2007)
PON1	C -107T	rs705379	0.48 (C)	W	710 (CVD)	-3.1/- 2.3 mg/dl (1/2 copies) ; p=0.006	(Blatter Garin et al. 2006)
PON1	Leu55M	rs85456	0.20 (T)	MA	741	p=0.02	(Chang et al. 2010)
SCARB1	Exon 8 C>T	rs5888	0.44 (T)	W	865 (P)	+1.9/2.7 mg/dl 1/2 copies;p=0.006	(Morabia et al. 2004)
SCARB1	C1050T	rs5888	0.49 (T)	W	546 (CVD)	+2.3 /+1.9 mg/dl (1/2 copies); p=0.03	(Boekholdt et al. 2006)

Table 1. Genetic Polymorphisms Associated With HDL-C. MAF=Minor Allele Frequency; Ethn.: A=Asians; AA=African Americans; Am=Amish; A-I=Asian Indian; B=Blacks; C=Chinese; CH=Caribbean Hispanics; In=Inuit; Ma= Malays; N=Netherlands; NHW=Non-Hispanic Whites; H=Hispanics; Hu=Hutteries; Tu=Turks; UK=United Kingdom; W-Bra=Caucasian Brazilians; W= Whites; Va=Various; Non-DM C0=Non diabetic control subjects; MI=Myocardial infarction; NGT=Normal glucose tolerance; DM= Diabetes mellitus; Ho Sta= Hospital staff; HBP= Hypertensive patients; He Ex=Health examination; Cor Ang=coronary angiography; hyperCH=hypercholesterolemia patients; CVD= Cardiovascular Disease; Co=Controls; Ho Co=Hospital based controls; GP=General Population; Meta= Meta Analysis; P=Population based; M= Males; F= females; + =increase; - = decrease; n.s.=not significant; see text for full gene names. Adapted from Boes et al. (2009) with permission from Elsevier.

2.1 Genetic variation in enzymes involved in lipid metabolism and HDL-C levels

Perhaps, the most notable gene in the HDL-C synthesis and metabolism pathways, whose variants have been consistently associated with HDL-C, is the cholesterol ester transfer protein (CETP), which is a key plasma protein that mediates the transfer of esterfied cholesterol from HDL to APOB containing particles in exchange for TG. Although complete loss of CETP function is rare and can yield HDL-C levels up to five times higher than normal (Klos and Kullo, 2007), three common polymorphisms (Table 1: TaqIB (rs708272); -

629C>A (rs1800775); Ile405Val (rs5882)) can all modestly inhibit CETP activity and have been consistently associated with higher HDL-C levels (Bernstein et al., 2003; Blankenberg et al., 2004; Boekholdt et al., 2005; Boekholdt and Thompson, 2003; Borggreve et al., 2005; Eiriksdottir et al., 2001; Freeman et al., 2003; Kathiresan et al., 2008a; Klerkx et al., 2003; Tai et al., 2003b; Thompson et al., 2008). The CETP gene is located on chromosome 16 (16q21).

Lipoprotein lipase (LPL) is an enzyme involved in lipolysis of TG-containing lipoproteins such as VLDL and chlyomicrons (Miller and Zhan, 2004), which generate free fatty acids (FFA) that can be taken up by the liver, muscle and adipose tissues (Kwan et al., 2007). Thus, LPL affects LDL levels directly (see Section 3.2) may only affect HDL-C levels indirectly (Lewis and Rader, 2005). The human LPL gene is located on chromosome 8 (8p22). Several LPL SNPs have been associated with HDL-C (Table 1) (Ahn et al., 1993; Corella et al., 2002; Holmer et al., 2000; Klos and Kullo, 2007; Klos et al., 2006; Komurcu-Bayrak et al., 2007; Lee et al., 2004; Nettleton et al., 2007; Senti et al., 2001; Wittrup et al., 1999); however, many of them are in strong linkage disequilibrium with each other (e.g., rs320, rs326, rs13702, rs10105606) (Boes et al., 2009; Heid et al., 2008).

Hepatic lipase (HL; LIPC) is a glycoprotein that is synthesized by liver cells (hepatocytes) and catalyzes the hydrolysis of TG and phospholipids (Miller et al., 2003). For example, after hydrolysis of TG by LPL, VLDL particles are reduced to IDL particles and can be further hydrolyzed by HL/LIPC to LDL or taken up by the liver (Kwan et al., 2007). The human HL/LIPC gene is located on chromosome 15 (15q21). Several HL/LIPC SNPs have been associated with HDL-C levels (Table 1) (Andersen et al., 2003; Costanza et al., 2005; de Andrade et al., 2004; Fang and Liu, 2002; Grarup et al., 2008; Iijima et al., 2008; Isaacs et al., 2007; Kathiresan et al., 2008b; Ko et al., 2004; McCaskie et al., 2006; Nettleton et al., 2007; Tai et al., 2003a; Talmud et al., 2002b; Whiting et al., 2005; Yamada et al., 2007). However, the most consistent associations have been observed for rs1800588 and rs2070895 and, several SNPs in the promoter region are in strong LD (Boes et al., 2009).

Endothelial lipase (EL; LIPG) is an enzyme expressed in endothelial cells that, in the presence of HL/LIPC, metabolizes larger (HDL_3) to smaller (HDL_2) HDL-C particles and increases the catabolism of APOA-I (see Section 2.3) (Jaye and Krawiec, 2004). EL/LIPG plays a role in the dyslipidemia component and, possibly, the yet to be established, proinflammatrory component of MetSyn (Lamarche and Paradis, 2007) (see Section 5.0). The human EL/LIPG gene is located on chromosome 18 (18q21.1). Several polymorphisms in EL/LPIG have been associated with HDL-C levels (Table 1) (Hutter et al., 2006; Ma et al., 2003; Mank-Seymour et al., 2004; Paradis et al., 2003; Tang et al., 2008; Yamakawa-Kobayashi et al., 2003). However, most of these SNPs have not been as well studied as those in CETP, LPL and EL; and, only the nonsynonymous SNP, rs2000813, has been consistently associated with HDL-C levels in African-American populations (Hutter et al., 2006; Tang et al., 2008; Yamakawa-Kobayashi et al., 2003).

In the presence of cofactor, APOA-I (see Section 2.3), lecithin-cholesteryl acyltransferase (LCAT), catalyzes the esterification of free cholesterol and, can metabolize larger HDL-C particles to smaller HDL-C particles (Klos and Kullo, 2007; Miller and Zhan, 2004). The human LCAT is located on chromosome 16 (16q22.1). Although mutations leading to complete loss of LCAT and marked (5-10%) reduction in HDL-C levels are rare and can cause cornea opacifications (fish eye disease) and renal disease (Garg and Simha, 2007), several common polymorphisms in LCAT have been associated, albeit inconsistently, with much more modest changes in HDL-C levels (Table 1) (Boekholdt et al., 2006; Miettinen et al., 1998; Pare et al., 2007; Zhang et al., 2004; Zhu et al., 2006).

Parroxanonase 1 (PON1), inhibits the oxidation of LDL (Mackness et al., 1991) and, therefore, may only indirectly affect antioxidant properties of HDL-C. The human PON1 gene is located on chromosome 7 (7q21.3). Several SNPs in PON1 have been associated with HDL-C levels, most notably, two nonsynonymous SNPs, rs662 and rs3202100, which are in strong LD, but results are inconsistent across studies (Table 1) (Blatter Garin et al., 2006; Hegele et al., 1995; Manresa et al., 2006; Rios et al., 2007; van Aalst-Cohen et al., 2005).

2.2 Genetic variation in receptors and transporters and HDL-C levels

Scavenger receptor class B, type 1 (SCARB1; SR-B1), which is highly expressed in liver and steroidogenic tissues (testes, ovaries, adrenal) (Cao et al., 1997), has been shown to participate in the uptake of HDL in animals by transferring cholesterol from the HDL-C particle and releasing the lipid-depleted HDL particle into the circulation (Acton et al., 1996; Miller et al., 2003). The human SCARB1 gene is located on chromosome 12 (12q24.31). Only a few studies have examined potential associations between SCARB1 polymorphisms and HDL-C levels (Table 1) (Boekholdt et al., 2006; Costanza et al., 2005; Hsu et al., 2003; Morabia et al., 2004; Osgood et al., 2003; Roberts et al., 2007). The most well studied polymorphism has been rs5888; however, the association with rs5888 and HDL-C levels was only significant among Caucasian (White, W) males in one study (Morabia et al., 2004), Amish females (Roberts et al., 2007) and Caucasian CVD patients (Boekholdt et al., 2006).

The LDL receptor (LDLR) and LDLR-related protein participate in the uptake of LDL and chylomicron remnants by hepatocytes (Kwan et al., 2007) and, therefore, may only indirectly affect HDL-C levels. The human LDLR is located on chromosome 19 (19p13.2). Although some common polymorphisms in LDLR have been associated with HDL-C levels (Table 1: (Costanza et al., 2005; Hegele et al., 1995; Yamada et al., 2008), their impact is likely greater on LDL-C levels (see Section 3.1).

The ATP-binding cassette transporter A1 (ABCA1), which is highly expressed in the liver, steroidogenic tissues and macrophages, plays a key role in 'reverse cholesterol transport' by mediating the efflux of cholesterol and phospholipids from macrophages to the nascent lipid-free, APOA-1 HDL particle (Cavelier et al., 2006; Miller et al., 2003). The human ABCA1 gene is located on chromosome 9 (9q31.1). Due to its functional importance, genetic variants in this gene have been well investigated but many of them are quite rare including the homozygous deletion that leads to Tangier's disease that is characterized by very low HDL-C levels (~5 mg/dl), orange colored tonsils, peripheral neuropathy and, sometimes, premature CHD (Garg and Simha, 2007). Several common polymorphisms have been fairly consistently associated with more modest changes in HDL-C levels but different variants appear to drive this association in different ethnic groups (Table 1) (Clee et al., 2001; Costanza et al., 2005; Frikke-Schmidt et al., 2004; Hodoglugil et al., 2005; Kathiresan et al., 2008b; Klos et al., 2006; Porchay et al., 2006; Shioji et al., 2004b; Whiting et al., 2005).

2.3 Genetic variation in apolipoproteins and HDL-C levels

Apolipoprotein A-1 (APOA1; APOA-I) is a ligand required for HDL-C binding to its receptors including SCARB1 and ABCA1 and, is an important cofactor in 'reverse cholesterol transport' (Miller et al., 2003; Remaley et al., 2001; Rigotti et al., 1997). The

human APOA1 gene is located on chromosome 11 (11q23-24). APOA-I is a major constituent of HDL particles and deletions leading to complete APOA-I deficiency are rare but lead to HDL deficiency (HDL-C <10 mg/dl) and sometimes CHD (Garg and Simha, 2007). Several common polymorphisms in APOA-I have been associated with more modest reductions in HDL-C but results across studies are inconsistent (Table 1) (Brown et al., 2006; Kamboh et al., 1999b; Larson et al., 2002; Shioji et al., 2004a).

Apolipoprotein A-4 (APOA4; APOA-IV) is a potent activator of LCAT and modulates the activation of LPL and transfer of cholestryl esters from HDL to LDL (Kwan et al., 2007). The human APOA4 gene is located on chromosome 11 near APOA1 (11q23) and is part of what is known as the APOA1/C3/A4/A5 gene cluster. Polymorphisms in APOA4 have not been as well studied; however, the nonsynonymous SNP, rs5110 (Gln360His), has recently been associated with reduced HDL-C levels in Brazilian elderly (Ota et al., 2011) and coronary artery calcification (CAC) progression, a marker of subclinical atherosclerosis, in patients with Type I Diabetes Mellitus (T1DM) (Kretowski et al., 2006). The rs675 polymorphism has been associated with reduced HDL-C levels in females with T2DM (Qi et al., 2007).

Apolipoprotein A-5 (APOA5; APOA-V) is located predominantly on TG-rich chylomicrons and VLDL and activates LPL (Hubacek, 2005). The human APOA5 gene is located on chromosome 11 (11q23) in the APOA1/C3/A4/A5 gene cluster. Several APOA5 SNPs have been associated with reduced HDL-C levels; and, perhaps, the most well studied and consistent associations have been observed for rs651821 and rs662799 (Table 1) (Grallert et al., 2007; Hubacek, 2005; Klos et al., 2006; Lai et al., 2003; Qi et al., 2007; Talmud et al., 2002a; Yamada et al., 2008; Yamada et al., 2007).

Apolipoprotein C-3 (APOC3; APOC-III) is an inhibitor of LPL and is transferred to HDL during the hydrolysis of TG-rich lipoproteins (Kwan et al., 2007; Miller and Zhan, 2004). The human APOC3 gene is located on chromosome 11 (11q23) in the APOA1/C3/A4/A5 gene cluster. Although several APOC3 SNPs have been identified and investigated, associations between these SNPs and HDL-C levels have been quite inconsistent (Table 1) (Arai and Hirose, 2004; Brown et al., 2006; Corella et al., 2002; Hegele et al., 1995; Kamboh et al., 1999a; Lahiry et al., 2007; Pallaud et al., 2001; Qi et al., 2007; Russo et al., 2001).

Chylomicron remnants, VLDL and IDL particles are rich in apolipoprotein E (APOE) and APOE is a critical ligand for binding to hepatic receptors that remove these particles from the circulation (Kwan et al., 2007). Mutations in APOE are well known to modify LDL-C levels; however, their independent influence on HDL-C levels remains controversial (Sviridov and Nestel, 2007). Nevertheless, associations between APOE SNPs and HDL-C levels in large scale studies have been fairly consistent (Costanza et al., 2005; Frikke-Schmidt et al., 2000; Gronroos et al., 2008; Kataoka et al., 1996; Srinivasan et al., 1999; Volcik et al., 2006; Wilson et al., 1994; Wu et al., 2007).

2.4 GWAS and HDL-C Levels

Results from genomewide association studies (GWAS) have confirmed associations between polymorphisms in viable candidate genes including CETP, LPL, HL/LIPIC, EL/LIPG, ABCA1, LCAT and the APOA1/C3/A4/A5 gene cluster and HDL-C levels (Boes et al., 2009). GWAS have also identified several novel putative loci, which are discussed in detail in a recent review (Teslovich et al., 2010).

3. Genetic variants in lipid metabolism and LDL-C levels

3.1 Genetic variation in enzymes, receptors and transporters and LDL-C levels

LDL-C is a widely accepted risk factor for atherosclerotic cardiovascular diseases. The most marketed drugs for lowering LDL-C are statins, which inhibit hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), the rate limiting enzyme in cholesterol synthesis that is normally suppressed (Endo, 1992). The human HMGCR gene is located on chromosome 5 (5q13.3-14). Only a few common HMGCR polymorphisms have been associated with LDL-C levels including rs3846662, which was identified through GWAS (Table 2) (Burkhardt et al., 2008; Hiura et al., 2010; Polisecki et al., 2008; Teslovich et al., 2010).

As mentioned above, the LDL receptor (LDLR) regulates the uptake of LDL and chylomicron remnants by hepatocytes (Kwan et al., 2007) and, the human LDLR gene is located on chromosome 19 (19p13.2). Familial (or monogenic) hypercholesterolemia (FH: OMIM No. 143890), which is due to mutations in LDLR occurring at a frequency of approximately 1 in 500 (heterozygotes) to 1 in 1,000,000 (homozygotes), is one of the most common inherited metabolic diseases and results in a reduced number of LDL receptors and, in heterozygotes, a 2- to 3-fold increase in LDL–C levels and, in homozygotes, complete loss of LDLR function and a greater than 5-fold increase in LDL-C (Garg and Simha, 2007). A few common polymorphisms in LDLR have been identified and associated with more modest changes in LDL-C levels, most notably, rs6511720, which was highly significantly associated with LDL-C in a recent meta analysis (Table 2) (Teslovich et al., 2010; Willer et al., 2008).

ATP-binding cassette transporters G5 and G8 (ABCG5/8) regulate the efflux of cholesterol back into the intestinal lumen and, in hepatocytes, the efflux of cholesterol into bile (Graf et al., 2003). The human ABCG5/8 gene cluster is located on chromosome 2 (2p21). A rare autosomal recessive mutation in ABCG5/8 leads to sitosterolemia characterized by xanthomas, premature atherosclerosis and other features (Berge et al., 2000). Only a couple of common variants in ABCG5/8 have been associated with LDL-C levels and a recent meta-analysis failed to find associations between ABCG5/G8 polymorphisms including, ABCG8 rs6544718, and plasma lipid levels (Table 2) (Jakulj et al., 2010; Teslovich et al., 2010)

3.2 Genetic variation in lipoproteins and LDL-C levels

Apolipoprotein B (APOB; main isoform: ApoB-100) is responsible for the recognition and uptake of LDL by LDLR, which clears approximately 60-80% of the LDL in 'normal' individuals with the remaining taken up by LRP or SCARB1 (Kwan et al., 2007). The human APOB gene is located on chromosome 2 (2p23-24). Familial defective APOB (FDB: OMIM No. 144010) is an autosomal codominant disorder due to mutations in APOB that are a bit more rare than FH mutations at approximately 1 in 500 to 1 in 700 resulting in lower LDL-C levels than in FH patients (Garg and Simha, 2007). Common polymorphisms have also been identified and associated with more modest changes in LDL-C (Table 2) (Haas et al., 2011; Teslovich et al., 2010; Waterworth et al., 2010; Willer et al., 2008).

As mentioned above, APOE is a critical ligand for binding chylomicron remnants, VLDL and IDL particles to hepatic receptors to remove these particles from the circulation (Kwan et al., 2007). The human APOE gene is located on chromosome 19 (19q13.2). The structural APOE gene is polymorphic with three common alleles, designated as ε2, ε3 and ε4 which encode for E2, E3 and E4 proteins, respectively. Although several APOE polymorphisms have been identified, the APOE ε4 allele has been the most consistently associated with CHD and LDL-C levels (Table 2) (Anoop et al., 2010; Chang et al., 2010; Eichner et al., 2002; Teslovich et al., 2010; Willer et al., 2008).

Gene	Polym.	rs Number	MAF	Ethn.	Sample Size	Results (Effect Size, p-value)	Reference
ABCG8		rs4299376	0.30 (G)	E	95,454 (Meta)	+2.75 mg/dl; $p=2x10^{-8}$	(Teslovich et al. 2010)
ABCG8	A632V	rs6544718		Va	982	p=0.02	(Jakuljl et al. 2010)
APOB		rs562338	0.18 (A)	Va	10,849	+4.89 mg/dl; $p=3.6 X 10^{-12}$	(Willer et al. 2008)
APOB		rs754523	0.28 (A)	Va	6,542	+2.78 mg/dl; $p=1.3 X10^{-6}$	(Willer et al. 2008)
APOB		rs693	0.42 (G)	Va	3,222	+2.44 mg/dl; p=0.0034	(Willer et al. 2008)
APOB	Thr98Ile	rs1367117	0.30 (A)	E	95,454 (Meta)	+4.05 mg/dl; $p=4x10^{-114}$	(Teslovich et al. 2010)
APOB		rs7575840	0.28 (T)	F	5054	0.131 $p= 3.88x10^{-9}$	(Haas et al. 2011)
APOB		rs515135	0.19 (A)	Va	982	$p=2.4X10^{-20}$	Waterworth et al. (2010)
APOE		rs4420638	0.17 (G)	E	95,454 (Meta)	+7.14 mg/dl; $p=9x10^{-147}$	(Teslovich et al. 2010)
APOE	Arg176 Cys	rs7412	0.06 (T)	N-HB	683	-22.52mg/dl; p< 0.0001	(Chang et al. 2010)
APOE	Cys130 Arg	rs429358	0.076 (T)	M-A	739	10.54mg/dl; p< 0.0001	(Chang et al. 2010)
APOC1		rs4420638	0.82 (A)	Va	10,806	+6.61 mg/dl; $p = 4.9 X10^{-24}$	(Willer et al. 2008)
APOE/ C1/C4		rs10402271	0.67 (T)	Va	6,519	+2.62 mg/dl; $p =1.5 X 10^{-5}$	(Willer et al. 2008)
LDLR		rs6511720	0.11 (T)	E	95,454 (Meta)	-6.99 mg/dl; $p=4x10^{-117}$	(Teslovich et al. 2010)
LDLR		rs6511720	0.90 (T)	Va	7,442	+9.17 mg/dl; $p =3.3 X 10^{-19}$	(Willer et al. 2008)
PCSK9		rs11206510	0.81 (C)	Va	10,805	+3.04 mg/dl; $p=5.4 X 10^{-7}$	(Willer et al. 2008)
PCSK9		rs2479409	0.30 (G)	E	95,454 (Meta)	+2.01mg/dl; $p= 2x10^{-28}$	(Teslovich et al. 2010)
PCSK9	A443T Ala443Thr	rs28362263	0.06 (A)	B	1750	95.5 vs. 106.9 mg/dl;p<0.001	(Huang et al. 2009)
PCSK9	C679X	rs28362286		B	1750	81.5 vs. 106.9 mg/dl;p<0.001	(Huang et al. 2009)
PCSK9	E670G	rs505151	0.11 (G)	W	691	P=0.001	(Chen et al. 2005)
PCSK9		rs11206510	0.81 (T)	EA	21,986 (Meta)	p=1.44E-05	(Dumitrescu et al. 2011)
SORT1		rs629301	0.22 (G)	E	95,454 (Meta)	-5.65 mg/dl; $p=1 x 10^{-170}$	(Teslovich et al. 2010)

Table 2. Genetic Polymorphisms Associated with LDL-C. See Table 1 legend.

3.3 Genetic variation in proteases and LDL-C levels

Proprotein convertase subtilisin-like kexin type 9 (PCSK9) is a serine protease that degrades hepatic LDLR in endosomes (Maxwell et al., 2005). The human PCSK9 gene is located on chromosome 1 (1p32.3). A mutation in PCSK9 results in an autosomal dominant form of hypercholesterolemia (OMIM No. 607786) with clinical features similar to FH patients (Garg and Simha, 2007). Over 50 variants in PCSK9 have been shown to affect circulating levels of cholesterol; however, most of these are relatively rare (see Davignon et al., 2010) for a complete list). The number of common polymorphisms in PCSK9 is substantially less with only a few SNPs having been associated with changes in LDL-C levels (Table 2) (Chen et al., 2005; Evans and Beil, 2006; Huang et al., 2009; Teslovich et al., 2010; Willer et al., 2008).

3.4 GWAS and LDL-C Levels

GWAS have confirmed associations between polymorphisms in viable candidate genes including APOB, APOE, LDLR and PCSK9, and have identified novel SNPs associated with LDL-C levels with strong biological plausibility including an inhibitor of lipase (ANGPTL3), see Section 4.1 and a transcription factor activating triglyceride synthesis (MLXIPL) see Section 4.2 (Teslovich et al., 2010).

4. Genetic variants in lipid metabolism and TG levels

Plasma triglycerides (TG) integrate multiple TG-rich lipoprotein particles, predominantly, intestinally synthesized chylomicrons in the postprandial state and hepatically synthesized VLDL in the fasted state. Therefore, not surprisingly, there is considerable overlap between genetic variants associated with HDL-C and LDL-C levels as well as TG levels. For example, the Global Lipids Genetics Consortium (GLGC) found that 15 of the 32 loci associated with TG levels were also jointly associated with HDL-C levels, explaining 9.6% of the total variation in plasma TG, which corresponded to 25–30% of the total genetic contribution to TG variability (Teslovich et al., 2010). However, the joint associations reported do not appear additionally adjusted for the other lipid phenotype. Furthermore, certain loci appear to be more strongly associated with one lipid phenotype over the other while others have similar effect sizes; and, genetic heterogeneity between loci clearly exists between major ethnic groups.

4.1 Genetic variation in aolipoproteins and TG levels

As mentioned above (see Section 3.2), APOB is the backbone of atherogenic lipoproteins and is located on chromosome 2 (2p23-24). A rare monogenic autosomal recessive disorder called homozygous hypobetalipoproteinemia and rare autosomal codominant disorder called familial hypobetalipoproteinaemia (HHBL and FHBL, respectively: OMIM No. 107730), characterized by very low (<5th percentile of age- and sex-specific values) of plasma TG (and LDL-C) levels, which are caused by rare mutations in APOB (Burnett and Hooper, 2008; Di et al., 2009). Although common APOB polymorphisms have primarily been associated with LDL-C levels (Benn, 2009), GWAS has revealed that a common SNP in APOB, rs1042034, is associated with TG (Johansen and Hegele, 2011; Teslovich et al., 2010).
Common polymorphisms in the APOA1/C3/A4/A5 gene cluster, located on chromosome 11 (11q23), have been associated with HDL-C levels (see Section 2.3) as well as TG levels (Teslovich et al., 2010; Willer et al., 2008). A SNP in the APOE gene, rs439401, has also been shown to be strongly associated with TG levels in a recent GWAS meta analyses (Johansen and Hegele, 2011; Teslovich et al., 2010).

z	Polym.	rs Number	MAF	Ethn.	Sample Size	Results (Effect Size, p-value)	Reference
ANGPTL3		rs2131925	0.32 (G)	E	96,598 (Meta)	-4.94mg/dl; $p=9x10^{-43}$	(Teslovich et al. 2010)
ANGPTL3		rs1748195	0.70 (G)	Va	9,559	7.12 mg/dl; $p=5.4x10^{-8}$	(Willer et al. 2008)
APOA5		rs964184	0.13 (G)	E	96,598 (Meta)	+16.95mg/dl; $p=7x10^{-240}$	(Teslovich et al. 2010)
APOA5/A4/C3/A1		rs12286037	0.94 (C)	Va	9,738	25.82 mg/dl; $p=1.6x10^{-22}$	(Willer et al. 2008)
APOA5		rs662799	0.05 (A)	Va	3,248	16.88 mg/dl $p=2.7x10^{-10}$	(Willer et al. 2008)
APOA5/A4/C3/A1		rs2000571	0.17 (G)	Va	3,209	6.93 mg/dl; $p=8.7x10^{-5}$	(Willer et al. 2008)
APOA5/A4/C3/A1		rs486394	0.28 (A)	Va	3,597	1.50 mg/dl; p=0.0073	(Willer et al. 2008)
APOE		rs439401	0.40 (C)	C	4.192	$p=2.2\times10^{-5}$	(Liu et al. 2011)
APOE		rs439401	0.64 (C)	Va	Meta	$p=5.5x10^{-30}$	Johansen et al. (2010)
LIPC/HL		rs4775041	0.67 (G)	Va	8,462	3.62 mg/dl; $p=2.9x10^{-5}$	(Willer et al. 2008)
LIPC/HL		rs261342	0.22 (G)	Va	Meta	$p=2.0x10^{-13}$	Johansen et al. (2010)
LPL		rs12678919	0.12 (G)	E	96,598 (Meta)	-13.64 mg/dl $p=2x10^{-115}$	(Teslovich et al. 2010)
LPL		rs10503669	0.90 (A)	Va	9,711	11.57 mg/dl; $p=1.6x10^{-14}$	(Willer et al. 2008)
LPL		rs2197089	0.58 (A)	Va	3,202	3.38 mg/dl; p=0.0029	(Willer et al. 2008)
LPL		rs6586891	0.66 (A)	Va	3,622	4.60 mg/dl; $p=5x10^{-4}$	(Willer et al. 2008)
LPL	S447X	rs328	0.90 (C)	EA	24,258	p=4.16E-30	(Dumitrescu et al. 2011)
LPL	S447X	rs328	0.10 (X)	Va	43,242	-0.15 (-0.12- -0.19) mmol/l	(Sagoo et al. 2008)
LPL	D9N	rs1801177	0.03 (N)	Va	21,040	0.14 (0.08-0.20) mmol/l	(Sagoo et al. 2008)
LPL	N291S	rs368	0.03 (S)	Va	27,204	0.19 (0.12-0.26) mmol/l	(Sagoo et al. 2008)
LPL		rs326	0.18 (G)	C	4,192	$p=2.3\times10^{-6}$	(Liu et al. 2011)
LRP1		rs11613352	0.23 (T)	E	96,598 (Meta)	-2.70 mg/dl $p=4x10^{-10}$	(Teslovich et al. 2010)
MLXIPL		rs17145738	0.12 (T)	E	96,598 (Meta)	-9.32 mg/dl $p=6x10^{-58}$	(Teslovich et al. 2010)
MLXIPL		rs17145738	0.84 (T)	Va	9,741	8.21 mg/dl; $p=5x10^{-8}$	(Willer et al. 2008)
MLXIPL		rs7811265	0.81 (A)	Va	Meta	7.91 mg/dl $p=9.0\times10^{-59}$	(Johansen et al. 2011)

Table 3. Genetic Polymorphisms Associated With TG Levels. See Table 1 legend.

Angiopoietin-like 3 protein (ANGPTL3) inhibits LPL catalytic activity but this process is reversible (Shan et al., 2009; Shimizugawa et al., 2002). A monogenic autosomal recessive disorder called familial combined hypolipidemia (FCH: OMIM No. 605019), characterized by very low TG levels, is genetically complex and poorly understood; however, mutations in ANGPTL3 are believed to play a role. Common polymorphisms in ANGPTL3, most notably, rs2131925, have been associated with more modest changes in TG levels (Johansen and Hegele, 2011; Keebler et al., 2009; Lanktree et al., 2009; Teslovich et al., 2010; Willer et al., 2008). Sequencing individuals in the Dallas Heart Study has identified several additional nonsynonymous ANGPTL3 variants affecting TG levels (Musunuru et al., 2010); however, these SNPs require further investigation in other populations.

4.2 Genetic variation in enzymes and transcription factors and TG levels

As mentioned above (see Section 2.1), LPL is an enzyme that hydrolyzes TG-rich particles in peripheral tissues (muscle, macrophages, adipose) generating FFA and glycerol for energy metabolism and storage (Goldberg, 1996). More than 100 mutations in LPL have been identified (Murthy et al., 1996); however, only a few common nonsynonymous SNPs have been consistently associated with TG levels including rs1801177, rs328 and rs268 (Mailly et al., 1995; Rip et al., 2006; Sagoo et al., 2008; Teslovich et al., 2010; Willer et al., 2008). Two SNPs, rs1801177 and rs328, have also been consistently associated with CHD; however, there is fairly strong LD between these SNPs, at least in Caucasians (Sagoo et al., 2008).

MLX interacting protein like (MLXIPL) locus encodes a transcription factor of the Myc/Max/Mad superfamily which activates, in a glucose-dependent manner, carbohydrate response element binding protein (CREBP) that is expressed in lipogenic tissues coordinating the subsequent activation of lipogenic enzymes such as fatty acid synthase (FAS) to convert dietary carbohydrate to TG (Iizuka and Horikawa, 2008). The human MLXIPL gene is located on chromosome 7 (7q11.23). Although initially identified through GWAS, the rs1745738 polymorphism has been replicated in other studies (Johansen and Hegele, 2011; Teslovich et al., 2010; Wang et al., 2008; Willer et al., 2008).

5. Genetic variants in dyslipidemia and the Metabolic Syndrome (MetSyn)

As mentioned in the Introduction (see Section 1.0), MetSyn is a clustering of traits including dyslipidemia as well as obesity, hypertension and insulin resistance/dysglycemia. Undoubtedly, there is complex interplay between genetic determinants of each of these traits and 'environmental' factors including those related to lifestyle (diet, exercise, sleep) and those related to toxin exposure. Due to space limitations, we focus only on the genetic determinants of dyslipidemia that overlap with MetSyn defined as a single, unifying trait and refer the reader to other reviews for genetic determinants of the other traits involved in MetSyn (Joy et al., 2008; Monda et al., 2010; Pollex and Hegele, 2006; Sharma and McNeill, 2006) and their interactions with lifestyle factors (Adamo and Tesson, 2008; Garaulet et al., 2009; Ordovas and Shen, 2008; Phillips et al., 2008) and toxins (Andreassi, 2009).

Lipoprotein related genes with common SNPs associated with MetSyn (as defined by NCEP ATP III and AHA/NHLBI criteria) and HDL-C, LDL-C or TG levels include APOA5 and APOC3 (Table 4) (Grallert et al., 2007; Joy et al., 2008; Miller et al., 2007; Pollex et al., 2006; Pollex and Hegele, 2006; Yamada et al., 2008). Enzymes involved in lipid metabolism with genetic polymorphisms that have also been associated with MetSyn (using the NCEP ATPIII criteria) appear limited to the nonsynonymous SNP in LPL, rs328 (Table 4) (Joy et al., 2008;

Komurcu-Bayrak et al., 2007). Several SNPs in the LDLR have been associated with MetSyn (using AHA/NHLBI criteria) and LDL-C or HDL-C (Joy et al., 2008; Yamada et al., 2008).

Gene	Polymorphism	rs Number	Ethn.	Sample Size	Results (p-value)	Reference	Comments (definition)
APOA5	-1131T→C		J	1788	p< 0.0009	(Yamada et al. 2007)	NCEP ATP III
APOA5	c.56C→G		C	3124	p=0.026	(Grallert et al. 2007)	NCEP ATP III
APOA5	-3A→G		J	2417	p< 0.0001	(Yamada et al. 2008)	AHA/NHLBI
APOC3	-455T→C		O-C	515	p=0.029*	(Miller et al. 2007) (Pollex et al. 2006)	*Women only NCEP ATP III
LDLR	2052TmC		J	2417	p=0.0005	(Yamada et al. 2008)	AHA/NHLBI
LPL	S447X		Tu	1586	p=0.04	(Komurcu-Bayrak et al. 2007)	NCEP ATP III
LPL		rs295	Va	1407	OR= 0.7; $p=2.1 \times 10^{-3}$	(Grassi et al. 2011)	NCEP ATPIII

Table 4. Genetic Polymorphisms in Lipid Metabolism Associated with MetSyn. See Table 1 legend. WHO= World Health Organization; NCEP ATP III=National Cholesterol Education Program Adult Treatment Panel III, IDF=International Diabetes Federation; AHA=American Heart Association; NHLBI=National Heart, Lung, and Blood institute.

6. Genetic variants in dyslipidemia and MetSyn: Future directions

Given the polygenic nature and multi-level complexity of Dyslipidemia and MetSyn, a better understanding of the genetic determinants of each intermediate (lower level) phenotype as well as the collective integration of these traits as unifying syndromes (higher/hierarchical level) is needed, which will require more elegant statistical modeling methods and, perhaps, a paradigm shift in the way in which we think about dissecting genetic and environmental factors in complex traits. As stated throughout this chapter, there is considerable overlap between genetic variants associated with HDL-C, LDL-C and TG levels as well MetSyn as a unifying trait. As a result, there is great need to understand not only the aggregate effects of multiple variants in each of these genes but to also understand how the effects of variation in one gene are modified in the presence of other genes.

Aggregate effects of multiple variants in genes affecting dyslipidemia and MetSyn related traits have included calculation of 'risk scores', which simply add the number of 'risk alleles' in a weighted or unweighted manner. For example, unweighted risk scores were constructed by summing the number of 'TG-raising' alleles at 32 loci and placed in 'risk bins' (categories) to show that higher risk scores were significantly associated with patients with hypertriglyceridemia (HTG) compared to controls (Johansen and Hegele, 2011; Teslovich et al., 2010). Increasing genotype risk scores comprised by summing risk alleles in 9 common SNPs were associated with decreasing HDL-C levels (Kathiresan et al., 2008a).

We have used the multivariate statistical framework of structural equation modeling (SEM) to evaluate multiple genetic determinants of MetSyn and aggregate effects of individual genes by modeling MetSyn as a second-order factor together with multiple putative candidate genes represented by latent constructs, which we mathematically defined by multiple SNPs in each gene (Nock et al., 2009b). Using this approach with the Framingham Heart Study (Offspring Cohort, Exam 7; Affymetrix 50k Human Gene Panel) data, we found that the CETP gene had a very strong association with the Dyslipidemia factor but little effect on MetSyn directly. Furthermore, we found that the effects of the CSMD1 gene diminished when modeled simultaneously with six other candidate genes, most notably CETP and STARD13. Work to identify the genetic determinants of 'Syndrome Z', modeled as a higher-order, unifying syndrome defined by 5 first-order factors (dyslipidemia, insulin resistance, obesity, hypertension, sleep disturbance) (Nock et al., 2009a) using the latent gene construct SEM approach is underway.

The use of other forms of 'causal modeling' (edge/node; integrative genetics) has been proposed (Lusis et al., 2008), particularly, to improve our understanding of differential effects by gender as well as to better understand how maternal nutrition and epigenetics affect MetSyn. Furthermore, a complex model for the genetic determinants of MetSyn associated phenotypes was recently proposed and, using gene enrichment analysis and protein-protein interaction network approaches, the retinoid X receptor and farnesoid X receptor (FXR) were identified as key players in MetSyn given their multiple interactions with metabolism, cell proliferation and oxidative stress (Sookoian and Pirola, 2011). However, more elegant kinetic models may be required to understand the true influence of genetic variants on Dsylipidemia and MetSyn given the presence of multiple feedback loops and reversible reactions (Bakker et al., 2010; Gutierrez-Cirlos et al., 2011).

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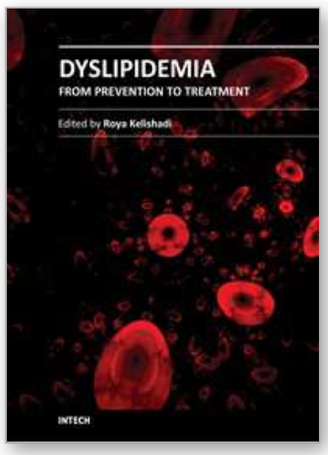

Dyslipidemia - From Prevention to Treatment
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Dyslipidemia has a complex pathophysiology consisting of various genetic, lifestyle, and environmental factors. It has many adverse health impacts, notably in the development of chronic non-communicable diseases. Significant ethnic differences exist due to the prevalence and types of lipid disorders. While elevated serum total- and LDL-cholesterol are the main concern in Western populations, in other countries hypertriglyceridemia and low HDL-cholesterol are more prevalent. The latter types of lipid disorders are considered as components of the metabolic syndrome. The escalating trend of obesity, as well as changes in lifestyle and environmental factors will make dyslipidemia a global medical and public health threat, not only for adults but for the pediatric age group as well. Several experimental and clinical studies are still being conducted regarding the underlying mechanisms and treatment of dyslipidemia. The current book is providing a general overview of dyslipidemia from diverse aspects of pathophysiology, ethnic differences, prevention, health hazards, and treatment.

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