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Phenotypes and Genotypes of High Density Lipoprotein Cholesterol in Exceptional Longevity

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Abstract

A change in the lipoprotein profile is a metabolic hallmark of aging and has been the target for modern medical developments. Although pharmaceutical interventions aimed at lipid lowering substantially decrease the risk of cardiovascular disease, they have much less impact on mortality and longevity. Moreover, they have not affected death from other age-related diseases. In this review we focus on high density lipoprotein (HDL) cholesterol, the levels of which are either elevated or do not decrease as would be expected with aging in centenarians, and which are associated with lower prevalence of numerous age-related diseases; thereby, suggesting a potential HDL-mediated mechanism for extended survival. We also provide an update on the progress of identifying longevity-mediating lipid genes, describe approaches to discover longevity genes, and discuss possible limitations. Implicating lipid genes in exceptional longevity may lead to drug therapies that prevent several age-related diseases, with such efforts already on the way.

Keywords

Genetics; Aging; CETP; APOC3; Longevity; HDL

Introduction

Aging is the major risk factor for age-related diseases. However, it has been observed that people with exceptional longevity are generally spared from age-associated diseases [1], despite these long-lived individuals having similar lifestyle habits as the general population [2]. While lowering low density lipoprotein (LDL) cholesterol or triglycerides (TG), using statins and other drugs, has not changed mortality significantly[3, 4] and has not affected the incidence of non-cardiovascular age-associated diseases[5], the challenge is to determine if increasing high density lipoprotein (HDL) cholesterol level will protect against age-related diseases and assure exceptional longevity. In support of such possibility is the observation that individuals with extended survival have higher HDL levels than would have been predicted based on their age and what is currently known about HDL physiology[6-9]. Families with longevity have also been found to have higher HDL levels than their peers in

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the general population, implicating heritability as the cause for elevated HDL levels[10]. Numerous genotypes have thus far been identified in various populations to be associated with HDL phenotype. Furthermore, the longevity and HDL related phenotypes and genotypes have been associated with decreased prevalence and incidence of multiple age related diseases, including hypertension, diabetes, cardiovascular disease, and Alzheimer's disease. Thus, HDL cholesterol phenotypes may be an inherited mediator of longevity that serves as a common link between longevity and protection from age-related diseases. Since the evidence is less robust that other lipoproteins play an important role in longevity, here we will review the epidemiologic and genetic evidence that associates longevity with HDL cholesterol.

Epidemiologic Evidence for the Association of HDL Cholesterol and Longevity

Numerous epidemiologic observations link HDL levels to longevity in various populations. In prospective studies, aging is known to be associated with a decline in HDL levels of approximately 1% per year[11, 12]. However, in cross-sectional analysis HDL levels do not change with age[11]. In fact, the HDL levels in groups with extended survival are comparable to those who are substantially younger[6, 8, 9]. This paradox suggests that the survivors have higher HDL levels, thereby implying that it promotes longevity.

In this review we will frequently refer to our well phenotyped group with exceptional longevity (defined as surviving to age 95), Ashkenazi Jews (AJs) in the Eastern United States (US). In AJ female centenarians, mean HDL levels were not significantly different compared to a control group of individuals without a family history of longevity, who was on average about 30 years younger [6]. The distributions of the HDL levels for males and females in our cohort are demonstrated in Figure 1. These are notable for centenarian HDL distributions that are skewed to the right. In addition, there is a shift to the right of the entire HDL distribution curves of the offspring of centenarians compared to the non-Ashkenazi control group, comprised of a representative cohort of US Caucasian females and males age 65 and older, sampled by the National Health and Nutrition Examination Survey 2009-2010. The Ashkenazi offspring and the NHANES 2009-2010 control groups were well matched on age and display meaningful differences in median HDL levels (Table 1). Similar findings were noted by other investigators, including the Leiden Longevity Study, which compared HDL cholesterol levels in Dutch sibling pairs with demonstrated longevity (females surviving at least to age 91 and males at least to age 89) to an unrelated control group who was on average 34 years younger[7].

The fact that the offspring of centenarian populations have higher HDL levels compared to the centenarians and to unrelated age-matched controls[6, 10], and the observation that centenarians have HDL levels that are comparable to the control, although HDL levels are known to decline with age, allows us to speculate that centenarians had higher HDL levels than the general population when they were 30 years younger. On the other hand, since not all studies demonstrate that offspring of long-lived parents have higher HDL levels than controls, also raises the possibility that individuals with exceptional longevity may have had

HDL levels that were comparable to the general population in their younger years, but may have experienced a slower decline in HDL later in life [7].

Additional evidence points to decreased prevalence and incidence of many age related diseases in association with longevity and higher HDL levels. Whereas aging has been noted to be the main risk factor for all age related diseases, individuals with exceptional longevity have been observed to have a similar prevalence of these diseases as a control group, who was on average 30 years younger [1]. At present, abundant epidemiological evidence supports an inverse relationship between HDL cholesterol levels and cardiovascular disease risk[13]. In the Framingham Heart Study, each additional 1mg/dL of HDL cholesterol was associated with a 2% and 3% decline in risk of coronary artery disease, in men and women, respectively[14]. In the group of Ashkenazi Jewish cohort, higher HDL levels were also associated with decreased prevalence of hypertension and cardiovascular disease[6], and protection from cognitive decline[15]. In a cross-sectional analysis of the Einstein Aging Study, which follows a heterogeneous population prospectively for the development of cognitive impairment, higher HDL levels were related to better memory and less dementia[15]. Higher HDL cholesterol levels have also been associated with better functional performance in individuals age 80 or older living in the community[16].

Thus, epidemiological evidence suggests that higher HDL levels may serve a protective role from numerous age related diseases, thereby contributing to longevity; although this presumption requires further validation in prospective and experimental studies.

Genetic Evidence for HDL Cholesterol and Longevity

Studies of longevity and HDL levels demonstrate that both may be predetermined by genetic factors. There is copious evidence for the inheritance of HDL[17, 18], with heritability estimates of up to 80%[17]. Also, there is mounting evidence from candidate gene approaches and unbiased Genomewide association studies (GWAS) associating specific genotypes with HDL levels and longevity, which, explains up to 12% of the HDL levels total variance[17, 19]. In addition, observational data of families with extended survival strongly suggests genetic predisposition as a major contributor to longevity, disease-free survival, and HDL.

The evidence for familial inheritance of exceptional longevity is substantial and suggests genetic basis for such phenomenon. In one analysis focusing on familial longevity, the parents of centenarians had an approximately seven-fold increased “risk” of reaching longevity (age 90-99) themselves, compared to parents of individuals without exceptional survival[1]. A comparable observation was made in a group of super-centenarians (age 110 or greater), with both their mothers and siblings having a significantly higher probability of surviving to age 90 years[20]. Nonagenarian siblings had a 41% lower risk of mortality compared to nonagenarians without familial history of longevity over a 3 year follow-up period[21]. Similarly, both parents and offspring of long-lived siblings exhibited lower mortality risks, with a 24% and 35% reduction in the standardized mortality ratios, respectively, compared to the general Dutch population[22].

Familial longevity may be mediated via lower susceptibility to age associated diseases, which may be inherited by the offspring from their parents. The offspring of parents with longevity exhibit a much lower prevalence of many age related diseases, including hypertension, cardiovascular disease, and diabetes mellitus, compared to offspring of parents without longevity[1, 21, 23]. In the Framingham Heart Study, offspring whose both parents survived to age 85 or older, had significantly lower Framingham Risk Score for coronary artery disease compared to offspring with one or no long-living parent[24]. Offspring of centenarians also demonstrate more favorable HDL profiles than their age and sex-matched peers. The female offspring of Ashkenazi Jewish centenarians have significantly higher HDL cholesterol levels compared to female offspring of Ashkenazi parents without longevity ($70\pm 17\text{mg/dL}$ vs. $59\pm 17\text{mg/dL}$, respectively)[6]. In addition, in a number of prospective analyses, offspring with longer living parents had lower risk of blood pressure, cardiovascular risk, and diabetes progression[24, 25]. Thus, a lot of longevity studies rely on a design involving families with a history of exceptional survival in order to discover longevity genes.

It has been observed that longevity-associated genotypes have a unique distribution in the population. These genotypes have been noted to be present at lower frequencies in the younger general population and increase in frequency with the rising age of the population (Figure 2)[26]. This change in the genotype frequency may be accounted for by the survival effect, with those possessing the longevity genotypes living longer than those without the longevity genotypes, with the longer survival, at least in part, presumably mediated by the longevity genotype; thereby raising the frequency of these beneficial genotypes in the older populations. An opposite genotype frequency distribution is hypothesized for the genotypes associated with aging; with a higher frequency present in younger populations and a lower frequency in those reaching older age.

Similar to longevity genotypes, age-associated increases in the frequency of genotypes related to higher HDL levels or unique HDL profiles have been identified (Figure 3). In fact, a number of these genotypes appear to be linked to both longevity and distinctive HDL profiles. For example, in the cohort of Ashkenazi Jewish centenarians, the frequency of homozygosity for the codon 405 valine allele of the cholesterol ester transfer protein (CETP VV genotype, rs5882), associated with larger HDL particle size, was significantly greater in centenarians than in younger Ashkenazi controls (24.8% vs. 8.6%, respectively)[6]. This finding was confirmed in a group of long-living Italians[27]. The prevalence of homozygosity for the -641C allele in the apolipoprotein C-3 (APOC-3) promoter (CC genotype, rs2542052), associated with higher HDL levels, was 25% in the Ashkenazi Jewish centenarians, compared to 20% in their offspring, and 10% in Ashkenazi population of similar age to the offspring, but without familial longevity[28]. These findings support the notion that HDL phenotypes are modulated by longevity genes and may contribute to extended healthy lifespan.

Lipoprotein Genotype and Longevity Phenotype

Apolipoprotein C-3 (APOC-3)—As previously mentioned, several of the identified longevity genotypes have been related to a variety of favorable HDL phenotypes. The

homozygous form of the APOC-3 (–641)C allele in the promoter region was associated with significantly higher HDL cholesterol levels compared to other genotypes at that locus (73.8 vs. 64.5 mg/dL, respectively), in females of Ashkenazi Jewish descent[28]. This genotype was also linked to lower APOC-3 levels in serum. In addition, APOC-3 concentrations were lower in Ashkenazi Jewish centenarians than younger Ashkenazim without a history of familial longevity[28], an expected finding given that APOC-3 CC genotype is more frequent in centenarians. In addition, APOC-3 (–641)C homozygosity was linked to improved insulin sensitivity (as measured by the homeostatic model assessment) and to lower prevalence of hypertension compared to other genotypes[28]. Furthermore, the survival of those carrying the APOC-3 CC genotype was significantly greater compared to those with other genotypes, with about 70% surviving to age 100 vs. 40%, respectively[28], although this result may have been influenced by the greater proportion of centenarians included in the homozygous group by virtue of them having a greater frequency of the APOC-3 CC genotype. In a cohort of the Lancaster Amish, a null mutation in APOC-3 (R19X), which results in lower APOC-3 levels, was associated with higher HDL levels and lower prevalence of subclinical atherosclerosis[29], further suggesting a protective role of genotypes linked to diminished APOC-3. On the other hand, a different APOC-3 gene polymorphism (at 3' untranslated region, 3238nt) was not related to HDL cholesterol levels; although, the APOC-3 activity was not determined for this polymorphism in the study[30].

APOC-3 is a major protein component of the triglyceride rich lipoprotein particles and a minor component of HDL[31]. It inhibits triglyceride hydrolysis by lipoprotein lipase (LPL) and interferes with clearance of triglyceride rich particles from plasma[32]. The inability of LPL to hydrolyze triglycerides results in failed maturation of HDL particles, accelerated clearance of HDL particles and lower HDL levels[31, 33]. Elevated levels of APOC-3 have also been correlated with atherosclerosis and endothelial dysfunction via mechanisms of delayed clearance of VLDL and LDL cholesterol particles, augmentation of arterial inflammation, and interference with normal nitric oxide function in endothelial cells, possibly via an insulin mediated mechanism[34, 35]. Given the proinflammatory and proatherosclerotic function of APOC-3, it would follow that lower APOC-3 concentrations associated with APOC-3 (–631) CC genotype would be expected to protect from atherosclerosis and other age related diseases, and result in higher HDL levels and prolonged survival.

Cholesterol Ester Transfer Protein (CETP)—A number of CETP genotypes have been associated with longevity and larger HDL and LDL particle sizes in various populations. The CETP 405VV genotype, which is found in greater frequency in the Ashkenazi Jewish centenarians compared to younger groups, was significantly related to lower CETP concentrations and larger HDL particle size (9.28 vs. 9.07nm in those homozygous for the CETP 405V allele vs. homozygous for the CETP 405I allele)[6]. In cross sectional studies, the CETP 405 VV genotype was also associated with a 20% lower prevalence of hypertension[36] and better cognitive function[15]. Some of these findings were validated in an Italian cohort of community dwelling adults age 85-100 years, in whom the CETP 405 VV genotype was associated with lower CETP activity and decreased prevalence of cardiovascular diseases[27]. In a large prospective study of age-associated

cognitive decline in a heterogeneous population, the Einstein Aging Study, homozygosity for CETP 405V was significantly related to lower risk of dementia (hazard ratio 0.28; 95% CI 0.1-0.85) and Alzheimer's disease (hazard ratio 0.31; 95% CI, 0.10-0.95), compared to CETP 405I homozygote carriers[37].

CETP is involved in the transfer of cholesterol esters from HDL particles to VLDL and LDL particles, in exchange for triglycerides[17], as part of the reverse cholesterol transport. The potential effect of this transport is an increase in the atherogenic cholesterol particles and a decline in HDL levels[17] and particle size. Lower CETP levels would be expected to result in larger HDL particles, which have been related to decreased risk of atherosclerosis, metabolic syndrome, diabetes, and greater antioxidative capacity[38]. Thus it would follow that the favorable phenotype observed in association with the CETP 405VV genotype may be mediated by large HDL particle size.

However, not all investigations of CETP I405V polymorphism have shown consistent results. Although larger HDL and LDL particle size has been associated with longevity in the long-living Dutch families, as well as in those surviving to age 90 without a familial history of longevity[7, 39], and the offspring of long-lived siblings had significantly larger lipoprotein particle sizes compared to controls [39], this phenotype was not explained by the CETP 405 VV genotype in these study populations. The frequency distribution of this genotype also did not resemble the longevity genotype in a group of Italian centenarians and middle-aged Greeks with familial longevity[40, 41]. In addition, a number of studies in European and Chinese populations[42-44] did not find associations between cognition and CETP I405V genotypes and a recent investigation in a cohort of European ancestry actually found the CETP 405VV genotype to be associated with an increased risk of Alzheimer's disease[45]. It is important to note, though, that these studies differed in methodologies from the previously mentioned ones and that the overall frequency of the CETP VV genotype in the Greek, as well as some of the other European study populations,[41, 45] was very low; thus highlighting the possibility that longevity genotypes may differ between different regions and ethnicities.

Another CETP polymorphism that has been associated with higher HDL levels in Chinese and Japanese centenarians and controls, but did not demonstrate "longevity gene" population frequency distribution is the *Taq1B* B2B2 genotype (rs708272)[46, 47]; thus, suggesting that is unlikely to be a longevity mediating genotype. Furthermore, the *Taq1B* allele is located in the CETP gene intron and its polymorphism is related to a silent base change; therefore, it is not likely to be a functional mutation and is probably related to high HDL levels by being in a linkage disequilibrium with some other unknown functional mutation[47]. Other mutations in the CETP gene, including in intron 14 (Int14A) which is associated with both CETP deficiency and elevated HDL levels, and in exon 15 (D442G, rs2303790), have not been consistently shown to be related to longevity and age-related diseases[46, 48, 49].

Other Genotypes—Investigations of other HDL-related gene polymorphisms, including paraoxonase 1 (PON1) Met55Leu (rs3202100) and Q192R (rs60480675), a gene whose function has been linked to inhibition of LDL oxidation and lower cardiovascular disease

risk[50], suggest an association with longevity[51, 52]. However, evidence that would link improved HDL activity to longevity is still lacking. A unique haplotype of the mitochondrial DNA, haplogroup F, has also been associated with longevity and higher HDL levels in a population of long-lived Chinese females; but, this genotype was not related to HDL levels in a control group and thus may not be mediating the observed phenotype [53].

Potential Mechanisms for HDL Mediating Longevity

Strong evidence exists for the inverse relationship between HDL levels and the risk of numerous age-related diseases. These include lower rates of cardiovascular disease, hypertension, dementia, metabolic syndrome, and cancer, among others[6, 13, 54-57]. Larger HDL particle size may also serve a protective role in safeguarding against the onset of cardiovascular disease, hypertension, and metabolic syndrome[6]. Protection from age related diseases in those with favorable HDL phenotypes may be mediated via HDL's anti-atherogenic, anti-inflammatory, and anti-oxidative functions, which may result in systemic improved endothelial function and decreased inflammation[38]. These effects would be expected to lead to overall decreased incidence of age related diseases and morbidity, culminating in prolonged survival and longevity. Thus, longevity in individuals with favorable HDL phenotypes and associated genotypes may result from a decline in the onset of common age-associated conditions. Although it is also possible that longevity in these individuals with unique HDL profiles and genotypes may be mediated by some other, non-disease related, mechanisms.

Limitations of Current Genetic Approaches

The reviewed studies point out the challenges encountered in genetic research. One of the main roles of genetic studies is to highlight important biological pathways. For example, the CETP I405V polymorphism was shown to be associated with low plasma levels of the CETP gene product, large HDL cholesterol particles size, and decreased prevalence of age-related diseases in some populations with longevity. Although this particular genotype may not be found in all populations with longevity, as a single genetic variant may be dependent on the genetic structure of the population, the more relevant and widely applicable concept would be whether the same phenotype is linked to longevity in varied populations. Hence, if larger HDL particle size and lower CETP activity would be demonstrated to be associated with longevity and decreased prevalence of age related diseases, then that would be a much stronger validation of research findings than mere attempts to validate specific genotypes. Therefore, analysis of genotypes alone may not hold the true answer for diverse populations; thus, geneticists need to overcome these limitations and not simply focus on genetic variants but also on phenotypes when studying groups of varied origins.

This concept was highlighted in a recent study by Voight et al., which looked at the effect of numerous single nucleotide polymorphisms (SNPs) in HDL controlling genes on the incidence of myocardial infarction [58]. Despite significant epidemiologic evidence for the association between HDL cholesterol levels and decreased risk of CVD, the investigators were unable to show that an isolated genetically raised HDL level decreased the risk of myocardial infarction[58]. However, the authors did acknowledge that the CETP gene

variation (rs3764261) was related to a 4% decreased risk of myocardial infarction; albeit this risk reduction may not have been solely the result of a raised HDL[58]. Thus, HDL cholesterol genotypes and phenotypes elucidated specifically from centenarian populations may have more relevance for age-related diseases and longevity than genetic variants discovered in the general population.

Effect of Pharmaceutical Interventions on HDL Cholesterol and Longevity

Given the epidemiological evidence for HDL's protection against CVD, a number of therapeutic strategies to raise HDL cholesterol levels have been tested or are currently under investigation in clinical trials. A large trial evaluating the effect of gemfibrozil on HDL level and CVD events, in men with low baseline HDL cholesterol and pre-existing coronary artery disease, found a 6% increase in HDL cholesterol level that was associated with significant reductions in coronary events and stroke[59-61]. Studies evaluating niacin found that although it reliably raised HDL cholesterol it did not consistently lower CVD events[62, 63]. Additional trials of investigational drugs are ongoing, including CETP inhibitors, such as anacetrapib and evacetrapib, which raise HDL levels meaningfully higher than the previously available therapies[64, 65]. Inhibition of APOC-3 is also being considered by some pharmaceuticals as a means to raise HDL cholesterol. Even though pharmaceutical methods to raise HDL show some promise in reducing the age-associated CVD, their effects are inconsistent. Furthermore, it remains unknown if these therapies protect from other age-related disorders and result in longevity. In fact, a trial of the CETP inhibitor torcetrapib was halted prematurely due to an increased number of cardiovascular and all cause mortality events associated with its use[66], despite a significant elevation in HDL cholesterol levels and particle size[67]; whereas, a trial of dalcetrapib was stopped early secondary to its lack of efficacy on CVD prevention[68]. The adverse effects of torcetrapib are thought to be due to the drug-induced rise in aldosterone levels and blood pressure; however, these effects are assumed to be caused by the drug's off-target action [66], rather than via its inhibition of CETP. This is supported by an observation that individuals with the CETP 405VV genotype, which is associated with lower CETP levels and activity, actually have lower blood pressure compared to those with higher CETP levels[36]. Thus, elevating HDL just by any mechanism may not confer the protective effects observed in centenarians and pharmaceutical interventions may need to be based on discoveries made in populations with longevity.

Remaining Questions and Future Directions

The majority of current evidence for the role of HDL in longevity comes from cross sectional analyses. Validation of these findings in large prospective studies would offer more definitive conclusions. In addition, the effects of interventions that raise HDL levels or increase HDL particle size on survival and disease incidence would demonstrate the direct effect of raised HDL levels and enlarged HDL particle size. As previously mentioned, one such intervention is presently being investigated in multiple trials, utilizing CETP inhibitors to raise HDL levels[64, 65] with the goal of reducing cardiovascular disease incidence, although their effect on longevity will not be known for quite some time. It is also important to focus on whether interventions that raise HDL cholesterol concomitantly decrease the

incidence of other age-related diseases, including dementia, diabetes, and hypertension, as has been observed in multiple association studies. Another question that remains is whether extended survival is associated with slowed age-related decline in HDL levels or significantly higher HDL levels at baseline, compared to individuals not enriched with longevity genotypes. Elucidation of additional mechanisms, including epigenetic modifications, which are currently investigated, may shed more light on the associations between HDL cholesterol and longevity.

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Figure 1.
Density distribution of HDL levels in female (A) and male (B) Ashkenazi Jewish centenarians, offspring and NHANES 2009-2010 control groups. Vertical lines represent the median HDL level for each group.
Jewish centenarians, offspring and NHANES 2009

Figure 2.

Age-associated frequency distribution in the population of aging genotypes, longevity genotypes, and genotypes not associated with lifespan. (from J Clin Endocrinol Metab. 2010;95(10):4493-500)[26]

Figure 3.
Age vs. percent frequency of favorable HDL-associated genotypes

Table 1

Mean age and median HDL cholesterol (HDL-C) levels for Ashkenazi Jewish cohort and NHANES 2009-2010 control.

	Proband	Offspring	NHANES	Proband vs. Offspring (p-value)	Proband vs. NHANES (p-value)	Offspring vs. NHANES (p-value)
Female						
n	357	240	267			
Mean age (yrs)	98.0±2.8	72.7±6.3	72.4±4.1			
Median HDL-C (mg/dL)	52	67	58	<0.01	<0.01	<0.01
Male						
n	123	215	288			
Mean age (yrs)	97.9±2.8	72.5±5.5	72.1±4.2			
Median HDL-C (mg/dL)	48	52	47	0.08	0.33	<0.01