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LIPID ABNORMALITIES AND CARDIOVASCULAR PREVENTION (G DE BACKER, SECTION EDITOR)

How Genomics Is Personalizing the Management of Dyslipidemia and Cardiovascular Disease Prevention

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Abstract

Purpose of the Review To summarize advances in genomic medicine and anticipated future directions to improve cardiovascular risk reduction.

Recent Findings Mendelian randomization and genome-wide association studies have given significant insights into the role of genetics in dyslipidemia and cardiovascular disease (CVD), with over 160 gene loci found to be associated with coronary artery disease to date. This has enabled the creation of genetic risk scores that have demonstrated improved risk prediction when added to clinical markers of CVD risk.

Summary Incorporation of genomic data into clinical patient care is on the horizon. Genomic medicine is expected to offer improved risk assessment, determination of targeted treatment strategies, and improved detection of lipid disorders causal to CVD development.

Keywords Genomics · Genetic risk score for coronary artery disease · Cardiovascular prevention · Genome-wide association studies · Polygenic lipid disorder

Introduction

Incorporation of genetic information into the diagnosis and management of lipid disorders and cardiovascular risk reduction is an important and well-recognized advancement in patient care. One of the biggest breakthroughs was the discovery of low-density lipoprotein (LDL) receptor mutations in patients with homozygous familial hypercholesterolemia (FH) by Brown and Goldstein in 1974 [1]. Additional mutations have since been discovered and genetic testing is now an option in the diagnostic approach of FH [2]. In fact, the Familial Hypercholesterolemia Foundation Expert Consensus Panel now recommends genetic testing on all patients meeting definite or probable clinical criteria for FH in hopes to improve detection and treatment [3••]. Similar use of genetic information is available for other lipid disorders, as well other conditions that may increase the risk of cardiovascular disease (CVD). This is especially helpful when identification of harmful mutations enables targeted treatment to reduce CVD risk. More recently, Mendelian randomization (MR) studies and genome-wide association studies (GWAS) have increased our understanding of genes causally related to and associated with, respectively, lipid disorders and CVD.

Increased focus on CVD prevention led to the development of guidelines that utilize laboratory data, imaging tests, comorbid diagnoses and other anthropometric parameters to help determine appropriate preventive strategies. Even with optimal implementation and patient adherence, risk still remains,

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and to an alarming degree for some patients. Genomics refers to the study of all, or a large proportion of the genome, as opposed to genetics, which is a more focused study of individual genes. The continued advancement in genomics is anticipated to yield improved assessment of CVD risk as well as strategies for additional risk reduction.

Current Applications of Genetic Information

Genetic testing for specific lipid disorders has been the predominant use of genetic information in the management of lipid disorders and CVD risk reduction to date. As previously mentioned, this largely began with the discovery of LDL-receptor (LDL-R) mutations in patients with FH in 1974 [1]. Identification of mutations in apolipoprotein B (apoB) and proprotein convertase subtilisin/kexin type 9 (PCSK9) followed as other causes of FH with autosomal dominant inheritance [4–6]. Genetic testing of LDL-R, apoB, and PCSK9 is frequently used for diagnosing FH, especially if there is a new index case and/or the diagnosis is uncertain based on clinical criteria alone. A similar, but more recent application of genetic information can be performed as part of the diagnostic work-up for familial chylomicronemia syndrome (FCS), a much rarer inherited dyslipidemia affecting an estimated 1–2 per million [7, 8]. FCS most classically yields a Fredrickson type I phenotype consisting of chylomicronemia and severe hypertriglyceridemia due to ineffective triglyceride metabolism by lipoprotein lipase (LPL). This often leads to recurrent bouts of acute pancreatitis. FCS was initially considered to be a monogenic autosomal recessive disease due to mutations in LPL or in one of four cofactors [9]. More recently, polygenic forms have been acknowledged, making genetic testing more complex [10]. Despite the recent inclusion of polygenic forms, testing for mutations in LPL and its four cofactors implicated in FCS is an option in the diagnostic approach.

Genome-Wide Association Studies

The advent of genome-wide association studies (GWAS) in the late 2000s has provided clear starting points to determine genetic contributions and potential therapeutic targets to cardiovascular risk factors and disease [11]. GWAS follow two classic epidemiological frameworks: case-control study, which compares the prevalence of single-nucleotide polymorphisms (SNPs) in cases to controls, and quantitative trait association, which compares mean values of a continuous phenotype between homo- and heterozygotes, to identify novel SNPs of varying levels of significance. Risk-associated SNPs can be present in coding regions (exons) or non-coding regions (introns) of DNA, may directly or indirectly act on the cardiovascular phenotype of interest or may serve as "tagging SNPs" that are in linkage disequilibrium with the true functional (disease causing) variants and loci that are not tested for in GWAS [12, 13].

To date, GWAS have identified several hundred SNPs for CVD and cardiovascular risk factors [14, 15••]. Traits identified include loci associated with coronary artery disease (CAD), lipids, type 2 diabetes mellitus, blood pressure, C-reactive protein, and body mass index [16]. This list continues to rapidly expand, especially within the last decade, as GWAS have captured more genome-wide significant SNPs by incorporation of large international consortiums and imputation from various catalogs (e.g., 1000 Genomes Project, UK Biobank, Million Veteran Program, cARDIoGRAMplusC4D, etc.) [17]. In fact, between 2017 and 2018, the number of loci associated with CAD more than doubled to 161 [15••]. While the clinical relevance of the majority of GWAS-discovered SNPs has yet to be elucidated, this finding affords great potential for new therapeutic targets and improved risk stratification.

Albeit promising, there are known limitations of GWAS-obtained evidence. First, GWAS tend to find small effect sizes [14, 18]. This translates into a need for understanding the complex interplay of loci and further studies to confirm associations. Small effect sizes do not mean GWAS lack utility. Case in point, *HMGCR* variants are only associated with small changes in LDL-C, yet drugs targeted at this pathway (i.e., statins) have large effects on LDL-C levels and disease risk reduction [18]. To date, the majority of GWAS focused predominantly in populations of European and Asian ancestry, leaving other ancestry groups underrepresented and may further exacerbate disparities in CVD [15••, 19]. In fact, no locus has reached genome-wide significance in African populations and only three separate loci have been replicated in Hispanic populations [15••, 20]. This limitation may contribute to both lack of predictability of genetic scores within these populations and more broadly contribute to lack of discovering rare frequency variants that have a large effect size or present new therapeutic targets [20]. These limitations can be overcome by larger, more diverse studies and pooling of cohorts [12].

Mendelian Randomization

The MR method uses random and naturally assorted genetic variants to determine if an association between a risk factor and outcome goes beyond association to causation [21••]. Emersion of large collections of genetic samples along with GWAS has made MR studies possible [22]. Often, studied variants are known to alter a measurable biomarker or target, such as LDL or a disease state, such as myocardial infarction [23]. Individuals are followed over time and then compared for outcomes of interest. The strength of an MR study lies in the random assortment of variants within a population, which occurs at conception during meiosis. This random assortment minimizes potential confounders, reverse causation, and other

biases [24]. Identification of potentially causal genes and variants via MR is rapidly improving the ability to assess individual risk and accelerating the search for viable drug targets [25].

Lipoprotein(a) (Lp(a)) is a prime example of how MR studies improve our understanding of causality and identification of treatment targets. Despite its discovery in 1963, the independent causal role of Lp(a) was difficult to prove. In the 1990s, as interest was waning in Lp(a) as independently causative of CVD, MR studies resurrected this interest by finding it to be causative [26, 27]. More recently, a MR analysis found that a decrease in Lp(a) of 101.5 mg/dL independently reduced Coronary Heart Disease (CHD) risk to a similar degree as a decrease in LDL-C by 38.67 mg/dL, which was previously found to correspond to a 20–25% decrease in CHD risk [28]. This role in causality may prove its importance in the therapeutic realm with the ongoing clinical trial of an antisense oligonucleotide (IONIS-APO(a)$_{Rx}$) to Lp(a) [29].

The list of genes evaluated by MR studies as causal in the risk for CVD and potential therapeutic targets continues to grow, especially among lipid-related targets, which includes those relating to LDL-C (*LDL-R, HMGCR, NPC1L1, PCSK9, APOB, ABCG5/G8, CETP, MTTP*), Lp(a) (*LPA*), and triglyceride-rich remnant particles (*LPL, APOC3, ANGPTL3, ANGPTL4, APOA5, TRIB1*), but interestingly not high-density lipoprotein cholesterol (HDL-C) [24, 25, 30, 31]. For HDL-C, this is especially important since multiple drug trials that raise HDL-C have failed to show a benefit, which is congruent with MR observations, suggesting HDL-C is a risk marker rather than a causal factor [25, 30]. Evaluation of inflammatory markers found a role for the interleukin-6 signaling pathway, but not for C-reactive protein or lipoprotein-associated phospholipase A2 [23, 32]. MR cohorts may also evaluate for causal phenotypes in CVD, which found education and BMI to have causal roles [33–35]. There are many other risk factors being analyzed, including those linked to hypertension and type 2 diabetes, that are not discussed here but may play an important role in precision assessment of patients. Table 1 summarizes key biomarkers and phenotypes studied by MR and their causal relationship with CAD.

Although MR studies have substantial potential, one should also be cautious of their limitations. Identification of causal pathways and risk variants need be understood within the plurality of genes conferring risk for an individual [21••]. As will be discussed, utilization of genetic risk scores substantially integrates the pleiotropic effects from an array of variants to better assess the precise risk and treatments for an individual [21••, 36].

Table 1 Biomarkers and phenotypes and their causal relationship with coronary artery disease according to Mendelian randomization studies

Causally related to CAD by MR	Not causally related to CAD by MR
LDL-C	HDL-C
TG-rich lipoproteins	CRP
Lp(a)	Fibrinogen
IL-6 signaling	Lp-PLA2
Blood pressure	Uric acid
BMI	Homocysteine

BMI body mass index, *CAD* coronary artery disease, *CRP* C-reactive protein, *HDL-C* high-density lipoprotein cholesterol, *IL-6* interleukin-6, *LDL-C* low-density lipoprotein cholesterol, *Lp-PLA2* lipoprotein-associated phospholipase A_2, *Lp(a)* lipoprotein(a), *MR* Mendelian randomization, *TG* triglyceride

Future Application of Genomic Medicine

Genetic Risk Score

The addition of genomic information to established clinical markers of CVD risk would enable improved calculation of a genetic risk score (GRS) as well as provide potential treatment targets based on which harmful alleles are identified. A GRS can be created by assigning a numerical value to each harmful allele that reflects its association with CVD as determined by GWAS, and then summing or averaging these values. GRSs have already been created for study purposes and new variants continue to be discovered. Study of the Atherosclerosis Risk in Communities (ARIC) cohort demonstrated improved CAD risk discrimination when a GRS containing 45 SNPs was added to clinical risk scores [37]. Other studies have also shown that use of a GRS improves CVD risk prediction of large cohorts such as the Framingham Heart Study [38, 39••, 40••]. Use of a GRS for CAD risk prediction appears to be beneficial in populations already known to be at greater CVD risk [41]; a retrospective study of 725 patients with an FH-causing mutation found that use of a GRS predicted risk of a CVD event that included an acute coronary event or coronary revascularization, peripheral vascular disease, or a cerebrovascular event. Those with a GRS calculated from 192 SNPs in the highest tertile had a significantly higher event rate than those in the lowest GRS tertile after adjustments were made for CVD risk factors, including lipid levels (40.9% vs. 24.7%, $p < 0.0001$).

While it is conceivable that the addition of a GRS into current prevention algorithms is on the horizon, several uncertainties need to be further elucidated. Components that are yet to be determined include construct of the optimal GRS that reflects risk of a multiethnic population, patient population selection, and additional genetic information of benefit, such as sequencing of genes related to drug metabolism. In addition to helping estimate risk with a GRS, incorporating genomic data will improve diagnosis of FH and other lipid disorders.

Genome Sequencing Selection

Adding genomic information to CVD prevention models requires selection of areas within the genome for sequencing

that are relevant to CVD and its risk factors. There are over 160 gene loci known to be associated with CAD, some of which affect lipid metabolism [42]. While there has been rapid discovery, this process is ongoing and some loci have yet to be discovered. This is especially true for certain ethnic groups, since many of the large genetic databases have come from European and Asian populations [15••]. For example, 9p21.3, a locus which has been determined to be associated with CAD, has not been found to be associated with increased CAD risk in those of African descent [43]. Due to GWAS, 9p21.3 variants were found to be associated with increased risk of CAD in certain ethnic groups through complex mechanisms, many of which are independent of effects on traditional risk factors, such as dyslipidemia and hypertension [44, 45]. The 9p21.3 example demonstrates how assessment of traditional risk factors does not fully define CVD risk. There are still genes related to lipid metabolism and lipid disorders that have yet to be discovered, which will likely have a place in the future optimal GRS.

Patient Selection in Cardiovascular Disease Prevention

The optimal patients for whom addition of genomic information to clinical parameters will improve risk prediction still needs to be determined. It is likely that the incorporation of genomic information will benefit all patients; however, some may derive greater benefit than others. In regard to primary prevention, patients with above average risk may benefit the most, for example, those with a concerning family history or comorbidities, such as diabetes or obesity. Incorporating genomic information into the primary prevention treatment strategy may enable medical providers to better assess how aggressive prevention measures should be for each patient, and/or give better insight into areas of risk to target.

A genomic approach to primary prevention for patients at average risk seems worthwhile for the same reasons as those stated for patients who are at increased risk, although cost-benefit analyses would need to be performed for both groups. It would likely be the case that those at average risk are less likely to have harmful variants identified on genome analysis; yet if found could lead to the same benefits of primary prevention strategies as listed above. Genomic assessment may be less likely to affect the level of aggressiveness of preventive strategies for patients with established CVD, since the most aggressive strategy is likely already in place. Rather, it may enable more accurate selection of targeted treatment(s) to optimally reduce risk. Cost-benefit analyses will need to be employed to inform on the level of benefit for secondary prevention.

Improved Diagnosis of Monogenic and Polygenic Lipid Disorders

Genetic testing is already an option for lipid disorders known to have monogenic inheritance such as FH and FCS [2, 46]. The Familial Hypercholesterolemia Foundation Expert Consensus Panel now recommends genetic testing on all patients meeting definite or probable clinical criteria for FH in an attempt to improve diagnosis and treatment of these patients given their substantial CVD risk [3••]. An additional aim is to improve prognostication, since those with an FH-causing mutation are at significantly higher CVD risk than those with a similar LDL-C who lack an FH-causing mutation [47]. One limitation is that clinically available genetic testing for such disorders only offers testing of genes previously identified. Obtaining patient genomic data will improve the diagnosis of lipid disorders both by finding new variants causing monogenic forms, as well as finding other combinations of alleles leading to polygenic forms.

Only recently have polygenic forms of some lipid disorders been considered [10, 48–50]. This is an important acknowledgement since many monogenic and polygenic cases benefit from the same treatment strategy. To improve diagnosing of FCS to include those without homozygous or compound heterozygous loss of function in one of the five known causal genes, a polygenic risk score was recently proposed by Stahel et al. using 14 loci related to triglyceride metabolism [51]. This was created in hopes of including patients without homozygous or compound heterozygous mutations in LPL or one of its four known cofactors, but with the same phenotype consisting of chylomicronemia, severely elevated triglycerides and risk of pancreatitis.

A polygenic risk score has not been proposed for FH; however, polygenic forms are being increasingly recognized. At this time, over 50 loci have been discovered that affect LDL-C levels [52]. Classic monogenic FH is now proposed to be considered a subtype of FH, with polygenic forms comprising about 50% of cases meeting diagnostic criteria [53]. Patient genome sequencing will therefore improve identification of genetic susceptibility to hypercholesterolemia and with widespread use; it is likely that more causative genes will be discovered in both monogenic and polygenic cases of FH.

Enabling Targeted Treatment Strategies

Genomic medicine offers identification of specific genetic loci causing or contributing to risk. Knowledge of which harmful alleles are present enables tailoring of the treatment strategy. For example, if genomic data reveal that a patient is at increased risk of abnormal triglyceride metabolism, this might lead to more emphasis on diet counseling to reduce triglyceride-rich lipoproteins. If harmful 9p21.3 variants are identified, highly aggressive CAD risk reduction should be

Table 2 Summary of important concepts gained from genome-wide association and Mendelian randomization studies

Causality of lipid metabolism genes	Genes predictive of LDL-C, triglyceride-rich lipoproteins, and Lp(a) levels are causally associated with CVD, while genes predictive of HDL-C are not.
GRS	GRS can predict CVD risk and can help guide statin therapy.
Timing of primary prevention	With GRS-guided risk assessment, individuals found to be at high genetic risk who would benefit from primordial primary prevention can be identified and started on aggressive risk-reduction therapy.
FCS-specific GRS	SNPs causative of hypertriglyceridemia have been identified, enabling calculation of a GRS specifically for FCS. This enables improved recognition of polygenic FCS.
FH-specific GRS	With increasing recognition of polygenic FH, an FH-specific GRS may soon become available.

CVD cardiovascular disease, *FCS* familial chylomicronemia syndrome, *FH* familial hypercholesterolemia, *GRS* genetic risk score, *GWAS* genome-wide association studies, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *Lp(a)* lipoprotein(a), *SNP* single nucleotide polymorphism

performed, at least for certain ethnic groups. LDL-C-lowering medications might have greater efficacy in patients with genetic abnormalities of the targeted protein, which appears to be the case in those with gain-of-function PCSK9 mutations treated with a PCSK9 monoclonal antibody [54].

More sophisticated treatments above lifestyle modifications and currently available medications may become available in the future to target certain damaging alleles as we continue to learn more from GWAS and MR studies. Genomic data would then be even more imperative. For example, a recent genome-modifying treatment consisting of an engineered meganuclease targeting PCSK9 demonstrated significant LDL-C lowering by up to 60% in Rhesus macaques [55]. Follow-up was about 1 year, demonstrating lasting effects in LDL-C-lowering. Alipogene tiparvovec encoded a naturally occurring gain-of-function LPL variant and was the first gene therapy approved for human use [56]. Despite reducing the number of episodes of acute pancreatitis, abdominal pain, and hospital admissions, the drug was eventually discontinued due to high cost and low demand after it was administered to only one patient with FCS in Germany [57]. If genome sequencing had been in widespread use at that time, more patients with LPL deficiency would have been diagnosed and potentially considered for this therapy. Continued advancement into both gene therapy development and patient genome sequencing may provide life-altering or life-saving targeted treatments for patients in the future.

Optimizing Drug Therapy

Pharmacogenomics refers to the role of the genome in drug metabolism and efficacy. Obtaining genomic data pertaining to drug metabolism would enable better tailoring of drug therapy, based on which drug metabolism alleles a patient possesses. One of the most studied genes in statin metabolism is SLCO1B1. It encodes the transporter protein OATP1B1, which is responsible for hepatocyte uptake of statins. A 2015 meta-analysis of nine case-control studies demonstrated an increased risk of statin-associated myopathy with the SLCO1B1*5 variant (OR 2.09, 95% CI 1.27–3.43, p = 0.003) and an even stronger association with statin-induced rhabdomyolysis or a tenfold CK elevation (OR 3.83, 95% CI 1.41–10.39, p = 0.008) [58]. Other variants of SLCO1B1 exist as do many other genes that metabolize drugs used to treat dyslipidemia, hypertension, CAD, and other CVD risk factors. Knowing which alleles for drug metabolism a patient has can help determine if certain drugs should be used at atypical doses or avoided altogether.

Obtaining a GRS in one large meta-analysis showed that in addition to enabling CAD risk prediction, the GRS also predicted benefit from statin therapy [38]. Those in the highest GRS quintile had a greater reduction in coronary events with statin therapy compared to those in the lowest quintile. This important trial was composed of patients from JUPITER and ASCOT as well as CARE and PROVE IT-TIMI 22, therefore representing primary and secondary prevention. A similar study focusing only on trials using statins in primary prevention found similar findings [59••]; looking at ASCOT, JUPITER, and WOSCOPS study participants, the quintile with the highest estimated risk based on a GRS derived from 57 common DNA sequence variants had a significantly greater reduction in CHD events with statin use as compared to other genetic risk groups. Combining the GRS and knowledge of drug metabolism alleles with previously established clinical markers of CVD risk will greatly enhance the selection of drug therapy for CVD prevention.

Conclusions

With the advent of GWAS, our understanding of the genetic contribution to lipid disorders and CVD has accelerated over the last decade. Table 2 summarizes what we have learned from GWAS and MR to date. There is still much room for discovery, especially in non-European and non-Asian populations, where GWAS have not been as robust. Building upon all that has been discovered to date will soon enable the incorporation of patient genomic sequencing into clinical practice.

Genomic sequencing will enable calculation of a GRS to help with CVD risk assessment, predict treatment response and guide-targeted treatment selection based on harmful variants identified, and improve the diagnosis of monogenic and polygenic lipid disorders. Because many genes found to be associated with CAD are unrelated to traditional risk factors, GRSs are expected to add significant improvement in risk assessment. Barriers to incorporation of genomic data include the need for further genomic research, especially for underrepresented ethnic groups, refining CVD risk assessment algorithms and cost-benefit analyses.

Compliance with Ethical Standards

Conflict of Interest Lane B. Benes, Daniel J. Brandt, Eric J. Brandt, and Michael H. Davidson declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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