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Genetic Risks of Cardiovascular Diseases

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Abstract: **Coronary Heart Disease (CHD) is the number one cause of death in the current world. Since numerous reasons heighten the risk of CHD, this review will focus only on genetic risk factors. Known for its ability to analyze and enhance chromosome mapping by garnering tons of human tests by its agnostic approach, conducting Genome-Wide Association Studies (GWAS) to examine genetic patterns in patients has perceived many undiscovered hidden genes. For instance, Sortilin is a gene vitally linked to cardiovascular diseases (CVD) risks and plasma LDL cholesterol levels. Moreover, GWAS could predict CVD risk furthermore and is beneficial for personalized medical treatment. Applying the understanding of genetics could create biomarkers that detect early stages of disease development and provide a precise diagnosis. Precise risk assessments and individualized treatment benefit projections are necessary. Accurate risk ratings, more potent drugs, and specialized evaluation of treatment are three tools to improve traditional risk estimation of CVD.**

Keywords: **Coronary Heart Disease; Genome-Wide Association Studies (GWAS); SORT1**

I. INTRODUCTION

The threat of Coronary Heart Disease (CHD) could be partially indicated by using Genetic Risk Scores (GRS) found in Coronary Artery Diseases (CAD) [1]. Note whether the GRS of CAD dominates the Coronary Artery Calcification (CAC) of CHD or whether the disparity between male and female CHD risks from utilizing the GRS of CAD is ambiguous [2]. Cardiovascular diseases such as coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic and congenital heart diseases, and venous thromboembolism lead to the number of global casualties [3]. Although most European nations have seen a reduction in deaths from CVD [4]. The decreasing mortality rate in Central and Eastern Europe (CEE) from CVD and stroke happens significantly slower. Genotyping and sequencing are key roles in disease diagnosis, therapeutic management, and prognosis markers for hypertrophic cardiomyopathy or familial hypercholesterolemia [5]. Genetic testing should be carried out in well-phenotyped individuals and coupled with a complete family appraisal to assist in interpreting and applying the results [5]. Cardiovascular studies pertained to molecular genetics technologies and expanded the understanding of chromosome mapping and the many unexplored genomes associated with primary etiology [5, 6]. Over the past two decades, our knowledge about genetics, how DNA variants co-operate, and how CVDs are inheritable could explain the dramatic growth of treatment [7]. This review aims to explore the relationship between genetic factors and risk of developing CVD.

II. CVD PATIENTS: GENOME-WIDE ASSOCIATION STUDY (GWAS)

Sortilin is the second example of a "new" gene discovered by GWAS (OMIM acc. No. 602458). The CELSR2/PSRC1/SORT1 gene cluster GWAS results were among the most crucial signal related to CVD risk and plasma LDL cholesterol levels [8-10]. In addition, the processes by which SORT1 affects plasma cholesterol levels in this instance were unclear (and remain so to date) [8, 11]. SORT1 encodes a multiligand sorting receptor primarily expressed in the liver and involved in intracellular trafficking [12]. Essential proteins involved in lipid metabolism, apolipoproteins E, B, and A5, with which they interact (reviewed by SORT1 affect VLDL transport through the hepatic Golgi apparatus and interact with PCSK9 to affect LDLR degradation [13, 14]. Lastly, it might function as a low-capacity alternate LDL receptor. Although the effects of SORT1 on plasma cholesterol levels and MI risk have been conclusively demonstrated and frequently validated, the data from animal models is inconsistent and often contradictory [15]. The roles of SORT1 appear to be highly complicated and contentious, and the precise molecular process is yet unknown [15]. Thus, the fundamental response has not been provided regarding the relationship between increased or decreased hepatic expression and an increased risk of

hypercholesterolemia and CVD risk [15, 16]. Despite the importance of SORT1 in determining plasma cholesterol levels at the population level, a considerable investigation was unable to identify any FH-associated mutation within this gene [17]. As this gene codes for the protein responsible for intracellular cholesterol transport, mutations within this gene may have devastating effects on the developing foetus [18]. This might explain why these mutations are not prevalent in the population. At this time, we cannot overlook FTO, arguably the most intriguing gene found by GWAS and has attracted interdisciplinary attention. GWAS revealed that FTO ("gene associated with fat mass and obesity"; OMIM acc. no. 610966) was related to both obesity and an increased risk of type 2 diabetes mellitus (T2DM) development [19]. The higher risk is attributable to clusters of variants in substantial linkage disequilibrium within the gene's first intron. The associations with body mass index (BMI) and T2DM were quickly confirmed in later studies, and the association with BMI was described in all significant ethnicities, except black Africans, in whom the frequency of the risky allele and the proportion of BMI variation explained (reviewed by) were significantly lower [20, 21]. The contribution of FTO variations to the risk of myocardial infarction was revealed immediately after the aforementioned first relationships, followed by identifying its function in renal failure, Alzheimer's disease, diabetic complications, and even in determining overall mortality [22]. Like ANRIL, the role of FTO is regulatory rather than structural or transport-related [23, 24]. Recent research suggests that the variations exert their effects through another gene in the same cluster (RPGRIP1-l/FTO/IRX3) as FTO, specifically IRX3 (Iroquois homeobox protein 3) [19]. In animal models, IRX3, whose promoter binds to enhancers in the first intron of FTO and whose expression is altered by tagged FTO variations, has also been linked to body weight [19, 22]. IRX3 is abundantly expressed in the pancreas, indicating vulnerability to FTO/IRX3 due to insulin secretion [19, 22]. The functions of FTO as a significant epigenetic modulator regulating nucleic acid methylation, telomere length determination, and functioning as a transcriptional coactivator have nevertheless been reported in the literature [23, 24]. It may be argued that the variations within the FTO 1st intron region are among the most significant and intriguing hits from the GWA period [19, 22]. It is essential to highlight that the GWAS-detected variations inside the known candidate genes from the age of "association studies" are frequently distinct (and more potent) than the variants reported in association studies [19, 22, 25].

III. GENE VARIATIONS INFLUENCING THE PROGRESSION OF CVD

GWAS taught us a lot about the genes of many non-communicable diseases such as CVD and its risk factors from tons of studies from human tests and chromosome mapping [26]. Because the GWAS technique takes form in an agnostic approach [26]. An example is a long noncoding regulatory RNA ANRIL (antisense noncoding RNA in the INK4 locus; located within the p15/CDKN2B-p16/CDKN2A-p14/ARF gene cluster) (OMIM acc. No. 613149) loci that are linked with the 30-35% risk increase in myocardial infarction (MI) in humans were detected in a “gene-free” region near chromosome 9p21.3 by SNPs (single nucleotide polymorphisms) via GWAS [27, 28]. Surprisingly, these detected variants show more correlation to a broader spectrum of non-communicable diseases such as different types of cancer, glaucoma, or even autism rather than traditional CVD risk factors like atherosclerosis except for diabetes [29, 30]. Realizing that these “gene-free” regions might be in quintessence for growing SNPs-related diseases, emphasizing the importance before further predicaments are necessary [31]. Sortilin (OMIM acc. No. 602458) a recently found gene thanks to GWAS within the CELSR2/PSRC1/SORT1 gene cluster waswas amongst the strongest threat connected to the risk of CVD and plasma levels of LDL cholesterol [13, 32].

IV. PREDICTING GENETIC HEART DISEASE RISK

The extensive population-based Heinz Nixdorf Recall research studied the link between CAD genetic risk score and CHD incidence [33]. The CAD genetic risk score was associated with incident CHD, with a more substantial effect in men and no effect in women; ii) the effect of the genetic risk score did not change after adjusting for Coronary Artery Calcification (CAC); iii) the CAD genetic risk score was associated with incident CHD only in the group with presence of CAC, with a more substantial effect in men and no effect in women; and iv) the CAD genetic risk score was associated with CAC [19, 34]. Multiple extensive CAD GWAS have led to the identification of new SNPs [14, 19, 20]. Few of them are newly reported and integrated into our study's genetic risk ratings. Similar to prior research, our investigation could demonstrate that the genetic risk score for coronary artery disease (CAD) derived from 70 SNPs is related to CHD incidence [35]. This impact was more pronounced in the group with the highest genetic risk, particularly men. These results are comparable to those of a previously published MESA research in which only males exhibited a greater CHD risk [34]. CAC is a well-established predictor of CHD occurrences independent of conventional risk variables. CAC possesses a genetic component and is highly inherited [33]. None of the prior investigations utilized CAC to determine if CAC may modify the link between the CAD genetic risk score and the incidence of CHD [36]. This study contains several strengths and weaknesses [37]. The study's strengths include its longitudinal design, extended follow-up period (11.6 3.7 years), strict set endpoint criteria, external

endpoint committee, and availability of data on CAC and other CHD-established RFs [38, 39]. In addition to its merits, the study also has several shortcomings [40]. The sample size of this study is its main restriction. Due to the small sample size, we could only stratify our research population based on CAC scores into two groups (CAC = 0 and CAC > 0) [15]. It would have been more beneficial to stratify the presence of CAC into low (1–99), intermediate (100–399), and high (400) risk groups [1]. More extensive studies based on CAC stratified analyses might assist in determining if the genetic risk score is superior to CAC in assessing the risk of CHD in each CAC stratified group [41]. More significant studies are necessary to evaluate the predictive capacities of the genetic risk score in this unclear risk category[41]. In addition, our analysis and the MESA trial revealed a similar non-significant connection between the genetic risk score and CHD in women; these findings require additional examination [42]. Two significant conclusions may be drawn from these observations. By conducting sex-stratified GWAS and incorporating chromosome X genetic variations in the GWAS, additional genetic variants for women have yet to be uncovered, and ii) the involvement of endogenous sex hormones [41]. Studies indicate that premenopausal women had a lower incidence and prevalence of cardiovascular disease than males of the same age [43, 44]. These gender disparities that benefit women appear to vanish after menopause [17]. Studies show that low ovarian hormone levels contribute to women's increased risk of cardiovascular disease [45, 46]. New observational research from MESA revealed that postmenopausal women with greater testosterone levels, lower estradiol levels, and a higher ratio of testosterone to estradiol had an increased risk for CHD events [47]. To determine if the interplay between sex hormones and the genetic risk score or genetic variations has a role in the risk assessment of CHD in women, larger-scale research on women is required [2]. Although our results suggest that genetic risk assessment in men in higher genetic risk groups may be helpful, additional, more extensive studies stratified by sex, different CAC risk groups, and intermediate-risk groups, as recommended by ACC/AHA, are required to evaluate the utility of genetic risk score in assessing CHD in men [47].

V. PERSONALIZED PREDICTION AND MANAGEMENT OF CVD RISK

CVD risk assessment

A CVD risk estimation algorithm's ultimate objective is to precise forecast who will develop CVD and when [48]. This capacity should not be confused with an algorithm's ability to estimate the proportion of a population that will acquire cardiovascular disease within a specific time [48]. Thus, population-based prediction and individualized prediction are distinct. According to the study, the algorithms successfully forecasted the number of CVD events that would occur in the population and accurately predicted low-risk individuals [19]. However, the three algorithms agreed with the CRCPH model marginally for people at high risk. This study demonstrates that the Framingham, ASSIGN, and QRISK2 CVD risk scores properly assess population-based hazards and identify low-risk people but cannot predict who will get CVD [49].

Predicting intervention benefits on an individual level may be a crucial technique in treating cardiovascular disease [50]. Recent study assessed the customized benefit of statin medication for a Dutch population of 2,428 individuals. The findings of a microsimulation model used to build a personalized calculator of improvements in total and CVD-free life expectancy with statin medication were compared with the CVD risk indicated by SCORE for each individual [51]. After an average of 18.3 years of statin medication, the authors noticed an average improvement of 0.3 years in life expectancy and 0.7 years in CVD-free life expectancy [49, 51]. These benefits of statin medication were deemed moderate, especially considering that the model neglected adverse effects [51]. As a result of its link with more outstanding CVD risk scores, statin medication is recommended as the patient's age increases [51]. However, due to conflicting risks of mortality from other illnesses, a higher 10-year risk of CVD does not always imply a more significant benefit from statin medication. As indicated in the research, a 55-year-old nonsmoking lady with a 10-year CVD mortality risk of 2% and a 65-year-old male smoker with a 10-year CVD mortality risk of 15% might both gain one year of CVD-free life expectancy with statin medication [52]. Twenty-five percent of the group with a low SCORE risk assessment had increases in CVD-free life expectancy equal to or greater than the median gain of individuals with a high SCORE risk calculation [53]. This contrast between CVD risk and treatment benefit may look slight, but it is crucial [54]. Statin therapy has demonstrated remarkable value for secondary prevention, but this study demonstrates the difficulty of deciding on primary prevention medication and the necessity for risk scores that also assess the individualized benefit of treatment [55, 56].

Current biomarker discovery

It was shown that branched-chain amino acids (BCAAs), valine, leucine, and isoleucine, as well as aromatic amino acids, tyrosine, and phenylalanine, might predict the development of diabetes, which is closely related to cardiovascular disease (CVD) [57]. Additionally, BCAAs and urea cycle metabolite plasma levels were used to predict CVD development [58]. Insulin resistance (IR) has been related to an elevated risk of cardiovascular disease (CVD), although it is not incorporated

into the existing risk-estimating algorithms. Utilizing metabolomics and lipidomics data, the Quantose IR method has been created to estimate IR [59, 60]. Quantose IR is independent of fasting insulin level and is based on hydroxybutyrate, 1-linoleoylglycerophosphocholine, and oleate [61]. This approach is an example of a potential improvement in the evaluation of IR by requiring just a fasting blood test, and it may boost the accuracy of the existing CVD risk-estimating algorithms [61, 62]. However, this has not been evaluated systematically. Recently, it was revealed that the lipid species TAG (54:2), CE (16:1), and PE (36:5) could improve the Framingham risk score in 685 individuals of the prospective population-based Bruneck cohort [63]. Including an extra three lipid species and removing HDL-cholesterol and total cholesterol from the Framingham risk score led to an improvement [64]. By including miR-126, miR-223, and miR-197 as biomarkers of CVD, the Framingham risk score has also been enhanced [65]. The addition of the SNP panel significantly increased the model's accuracy compared to a Cox proportional hazard model based on conventional risk variables [66]. Thus, omics-derived biomarkers of CVD have already demonstrated significant improvements over the conventional risk scores predicted by the existing algorithms [67, 68]. Nonetheless, the advantages are likely minor [69].

VI. CONCLUSION

In conclusion, each patient must understand his or her risk of cardiovascular disease (CVD) and the likely benefit of treatment to weigh it against any potential side effects. Therefore, accurate risk scores and personalized predictions of treatment benefits are required. As demonstrated, conventional risk estimation methods can be enhanced in this context. In CVD prevention, three tools are desperately needed: accurate risk ratings, more effective medications, and tailored evaluation of treatment benefits. Ideally, a systems medicine approach would benefit all of these areas. The CAD genetic risk score could help predict CHD risk, at least in men in the higher genetic risk group. However, it does not outweigh the value of the CT-based quantification of CAC, which works independently on both men and women and allows for better risk stratification in both sexes.

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