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Genetics in Peripheral Artery Disease

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Abstract

Besides traditional risk factor, it has been proved that genetics and gene–environment interaction have a possible independent role in the development and progression of peripheral arterial disease (PAD). Knowledge about such genetic factors will increase our understanding about pathophysiologic mechanisms of PAD and could facilitate the therapeutic approaches. Human genetics has gone through an advanced improvement and it increases our chance to acquire better diagnostic and therapeutic approaches. In this chapter, we try to provide an update on the genetics of PAD, which is mostly about genome-wide association studies, linkage analyses, heritability, candidate gene studies, and epigenetics. Finally, we discuss challenges and future developments of researches in PAD genetics.

Keywords: peripheral arterial disease, genetics, genome-wide association study, linkage analyses, heritability, candidate gene studies, epigenetics

1. Introduction

Common cause of PAD is atherosclerosis. Besides environmental risk factors (e.g., smoking, gender, age), some heritable risk factors are described for atherosclerosis. These are included hyperlipidemia, hypertension and diabetes mellitus. A reliable genetic marker could identify those individuals with PAD and accelerate their treatment. Besides, finding new genetic targets uncover new insights to the pathophysiology of PAD, and consequently new target for the cure. Earlier studies suggested heritability of PAD [1–4]. One study on monozygotic and dizygotic pairs revealed that with the similar environmental risk factors 48% variability of Ankle brachial Index (ABI) could be explained by additive genetic effects [2]. GENOA study

(Genetic Epidemiology Network of Arteriopathy) and the Framingham Offspring cohort study also found heritability in ABI variations [3, 4]. The degree of genetic variations on the PAD, regardless of the influences of other risk factors, remains to be revealed.

2. Genetic studies

Table 1 demonstrates comparisons between different genetic tests.

2.1. Linkage analysis

Genetic linkage analysis has the power to identify parts of genome that contain genes that could be inherited together. In this kind of genetic study, low resolution genome scanning investigates for genetic markers (microsatellites and Single nucleotide polymorphisms-SNPs) and that are pass to the next generation with the phenotype of interest. The results express in logarithm of the odds (LOD). Positive LOD indicates that co-segregation of two genetic markers is more likely, and negative LOD favors that likelihood less likely. It is advisable to consider LOD more than three statistically significant [5]. Next step is then to map neighboring region of the genome with tied association between genetic marker and phenotype.

Three studies demonstrated relation between different loci and PAD [3, 6]. First Gudmundsson and colleagues [6], identified a locus as “PAOD1” on chromosome 1p31 (LOD = 3.93; $p = 1.04 \times 10^{-5}$) conferring susceptibility to PAD even after nullifying the effects of diabetes mellitus, hypertension and hyperlipidemia. Interestingly, the genes responsible for PAOD1 did not identified which is not surprising based on the difficulties for analyzing genetic background of a complex disease such as PAD. Another study demonstrated the association of ankle-brachial index (ABI) with 250 microsatellite markers on chromosomes 1p, 6q, 7q, and 10p in 1310 African Americans and on chromosomes 3p and 3q in 796 non-Hispanic whites [3]. This study was also unable to demonstrate any evidence of linkage to the PAD trait.

Genetic test type	Advantages	Disadvantages
Single gene/panel gene sequencing	Cost; no off-target incidental findings	Low sensitivity
Oligonucleotide microarray	High resolution, good copy number detection	No detection of balanced rearrangements
Genome sequencing	Full coverage of DNA sequence	Cost, turnaround time, analytical challenges, inaccurate for SNPs with lower frequency
GWAS	novel marker finding	high participants number
Linkage	studying different areas across the genome, analyzing multiple genetic markers at the same time	It needs a high participants number with several affected generations, less helpful for complex disorders

Table 1. Comparison of different genetic tests for PAD genetics analysis.

Although, linkage analysis does not require specific candidate gene and scans full genome, it did not show promising results. That could be related to lack of large family pedigrees and polygenic nature of PAD. Linkage analysis cannot identify the genetic contributions arise from many genes each with small effect sizes.

2.2. Genome-wide association study

In this observational study, a genome-wide set of genetic variants (SNPs) can be screened in a large cohorts of patients. This approach determines the associations between SNPs and specific phenotype compared to control individuals. Unlike linkage analysis, GWAS has the ability to detect modest genotypic effects.

In one study rs10757278 SNP at 9p21 was found to be associated with PAD (OR = 1.14, $p = 6.1 \times 10^{-5}$), but exclusion of known CAD cases from sample sets reduced the effect of this variant significantly (OR = 1.09, $p = 0.075$) [7]. Another similar study showed an association between 9p21 SNP (rs 1,333,049) with severity and prevalence of PAD [8]. A Japanese study on 785 PAD and 20,134 control individuals found rs9584669 in IPO5/RAP2A related protein 2A (OR = 0.58, $p = 6.78 \times 10^{-14}$), rs6842241 in endothelin receptor type A (ENDRA gene; $p = 5.32 \times 10^{-9}$), and rs2074633 in histone deacetylase 9 (HDAC9 gene; $p = 8.43 \times 10^{-8}$) loci with susceptibility to PAD [9]. Thorgeirsson et al. identified a common variant (rs1051730) in the nicotinic acetylcholine receptor gene cluster on chromosome 15q24 with higher risk for PAD (OR = 1.19, $P = 1.4 \times 10^{-7}$) [10]. A GWAS study found rs7025486 at 9q33 associated with PAD (OR = 1.14, $p = 3.9 \times 10^{-5}$) [11]. An investigation performed on 699 PAD and 1540 Japanese controls identified rs1902341-A to have a strong association with PAD (OR = 1.31, $p = 4.7 \times 10^{-7}$) [12]. A recent meta-analysis with a total of 41,692 participants of European ancestry demonstrated that rs10757269 at 9p21 had the strongest association with ABI and achieved genome-wide significance ($p = 2.46 \times 10^{-8}$) [13].

After above mentioned meta-analysis, one study investigated 537,872 SNPs in 1641 PAD and 1604 control individuals in The Electronic Medical Records and Genomics consortium (eMERGE)-based GWAS of PAD [14]. They revealed that rs653178 in the ATXN2-SH2B3 locus was significantly associated with PAD (OR = 1.22, $p = 6.46 \times 10^{-7}$). Another outcome of this study was that neither loci was linked to PAD after investigation of prior known SNPs related to PAD. eMERGE analyses of PAD GEWAS results could not reveal any strong associations between SNPs and PAD by investigating of mitochondrial SNPs and haplogroups in 1652 PAD and 1629 control individuals [15].

2.3. Candidate gene studies

This kind of study focuses on differences in allele frequency of a known specific variant between cases and controls among unrelated individuals. With ability for finer mapping of the causal variant, association studies demonstrate greater power to detect modest genetic effects. Generally, search of insertions, deletions, and individual SNPs among cases and controls points out to genes to be associated with the development of atherosclerosis and changes

in various vascular biology pathways such as lipid metabolism [16], hemostasis [17–21], homocysteine [22–24], inflammation [25, 26], angiotensin converting enzyme [27], leukocyte adhesion [28], platelet activation and aggregation [29, 30], endothelial function [31, 32], and smooth muscle cell migration. A recent meta-analysis of around 50,000 SNPs and across about 2100 genes found only three SNPs associated with ABI or PAD [33]. They demonstrated that rs2171209 in SYTL3 ($p = 6.02 \times 10^{-7}$) (originally linked to lipoprotein (a)) and rs290481 in TCF7L2 ($p = 7.01 \times 10^{-7}$) (linked to diabetes mellitus type 2) were significantly associated with ABI and CYP2B6 ($p = 4.99 \times 10^{-5}$) (linked to smoking behavior) was associated to PAD.

2.4. Epigenetics

By definition, epigenetics is a science of long-lived or even hereditary modification of gene function without alteration of DNA sequence. In epigenetics, DNA could go through methylation, histone post-translational modifications, or microRNAs (miRNA), long non-coding RNA (lncRNA) mechanisms [34, 35]. miRNAs are small (≈ 22 nucleotides) single-stranded RNAs that inhibit translation of mRNA after binding to a target gene. Each miRNA can regulate several genes, because they do not require 100% base pair match. lncRNAs defined as more than 200 nucleotide long transcripts with function other than translation to protein.

Epigenetic changes have been described in association with some PAD risk factors [36, 37]. Hyperhomocysteinemia induces DNA methylation and could contribute to development and progression of PAD [36]. DNA hypomethylation caused by smoking has been reported [37].

Most of the epigenetic studies relevant to PAD are currently about miRNAs. There are two approaches to explore the role of miRNA in PAD. They have involved either a small number of candidate intracellular miRNA which are known for their role in vascular diseases or the measure of a large cluster of miRNAs by microarrays. A miRNA SYBR Green Real-Time PCR assessed the alteration of miR-130a, miR-27b and miR-210 expression in PAD [38]. A whole-genome miRNA transcriptome profiling revealed downregulation of 12 miRNAs in PAD compared to controls [39]. Later, the same research group detected significant downregulation of miR-15a, miR-196b, and let-7e and upregulation of miR-411 in 40 PAD and 40 control individuals [40].

Alterations in mitochondrial DNA (mtDNA) were proposed as a pathway for myopathy in PAD [41]. Mitochondrial dysfunction could be as a result of bouts of ischemia in these patients which causes damage to mitochondrion (mitochondriopathy).

2.5. Whole genome/exome sequencing

While massively parallel sequencing has not been performed on PAD patients specifically, some results from researches on atherosclerosis could be attributed to PAD. In one study, exonic regions of two persons with the early atherosclerosis were sequenced with next generation sequencing platform, and they revealed a rare missense mutation (Ser818Cys) in

INO80D, a subunit of the human INO80 chromatin remodeling complex [42]. INO80 complex is involved in cardiovascular physiology and development [43]. Another study repeated this result in two patients with aortic hypoplasia, diffuse atherosclerosis, and PAD.

2.6. Mendelian randomization

This epidemiologic study design incorporates genetic results into epidemiologic methods. Mendelian randomization studies offer evidence for causal relations between risk factors and disease outcome.

Mendelian randomization has been used to examine the relations between polymorphisms of specific genes and the prevalence of coronary heart disease or myocardial infarction [44]. Recently, it is demonstrated that each standard deviation (SD, 2.76 points) increase in body mass index (BMI)-composite genetic risk score was associated with 0.43 in BMI and an odds ratio for PAD of 1.17 [45].

3. Discussion

As multiple atherogenic pathways are involved in the pathophysiology of PAD, a profound monogenic effect is unlikely [46]. Environmental influences such as age, smoking, sport, ethnicity, and diabetes mellitus status besides genetic effects could vary the outcome for this disease. GWAS results are not comprehensive. It could be due to modest effect of susceptible variants. To power GWAS analysis, large sample sizes are needed. GWAS results so far revealed limited results. Two linkage studies did not demonstrate breakthrough to identify significant mechanisms behind inheritance of PAD. SNPs association studies have provided weak and/or conflicting findings results. Next generation sequencing and epigenetics seem to provide some promising future. Whole-genome or exome sequencing or NGS-based RNA-sequencing has identified new causative links between new genes and PAD. It is imperative to merge deep sequencing data of the DNA findings with epigenetic data to find more interesting results. This is challenging as these methods produce huge amount of data to analyze. Environmental-Wide Association Study demonstrates gene-by-environment interactions. This new method to study inter-relation between environment and genomics was a topic in ascertaining causality in type II diabetes mellitus [47]. They showed that the pesticide heptachlor epoxide was associated with type II diabetes mellitus. This new method has some places in gene-environment studies in PAD.

In the future, we may apply personalized medicine on the basis of genetic analysis and treat the patient by specific therapeutic agents.

Conflict of interest

All authors declare no conflict of interest.

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