Chapter 8

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 increases 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 deacylase 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 (mitochodriopathy).

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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References

[1] Allison MA, Criqui MH, McClelland RL, Scott JM, McDermott MM, Liu K, et al. The effect of novel cardiovascular risk factors on the ethnic-specific odds for peripheral arterial disease in the multi-ethnic study of atherosclerosis (MESA). Journal of the American College of Cardiology. 2006;**48**:1190-1197. DOI: 10.1016/j.jacc.2006.05.049

[2] Carmelli D, Fabsitz RR, Swan GE, Reed T, Miller B, Wolf PA. Contribution of genetic and environmental influences to ankle-brachial blood pressure index in the NHLBI twin study. American Journal of Epidemiology. 2000;**151**:452-458. DOI: 10.1093/oxfordjournals.aje.a010230

[3] Kullo IJ, Turner ST, Kardia SL, Mosley Jr TH, Boerwinkle E, de Andrade M. A genome-wide linkage scan for ankle-brachial index in African American and non-Hispanic white subjects participating in the GENOA study. Atherosclerosis. 2006;**187**:433-438. DOI: 10.1016/j.atherosclerosis.2005.10.003

[4] Murabito JM, Guo CY, Fox CS, D'Agostino RB. Heritability of the ankle-brachial index: The Framingham offspring study. American Journal of Epidemiology. 2006;**164**:963-968. DOI: 10.1093/aje/kwj295

[5] Lander E, Kruglyak L. Genetic dissection of complex traits: Guidelines for interpreting and reporting linkage results. Nature Genetics. 1995;**11**:241-247. DOI: 10.1038/ng1195-241

[6] Gudmundsson G, Matthiasson SE, Arason H, Johannsson H, Runarsson F, Bjarnason H, et al. Localization of a gene for peripheral arterial occlusive disease to chromosome 1p31. American Journal of Human Genetics. 2002;**70**:586-592. DOI: 10.1086/339251

[7] Helgadottir A, Thorleifsson G, Magnusson KP, Gretarsdottir S, Steinthorsdottir V, Manolescu A, et al. The same sequence variant on 9p21 associates with myocardial infarction, abdominal aortic aneurysm and intracranial aneurysm. Nature Genetics. 2008;**40**:217-224. DOI: 10.1038/ng.72

[8] Cluett C, McDermott MM, Guralnik J, Ferrucci L, Bandinelli S, Miljkovic I, et al. The 9p21 myocardial infarction risk allele increases risk of peripheral artery disease in older people.

Circulation. Cardiovascular Genetics. 2009;**2**:347-353. DOI: 10.1161/CIRCGENETICS.108.825935

[9] Matsukura M, Ozaki K, Takahashi A, Onouchi Y, Morizono T, Komai H, et al. Genome-wide association study of peripheral arterial disease in a Japanese population. PLoS One. 2015;**10**:e0139262. DOI: 10.1371/journal.pone.0139262

[10] Thorgeirsson TE, Geller F, Sulem P, Rafnar T, Wiste A, Magnusson KP, et al. A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. Nature. 2008;**452**:638-642. DOI: 10.1038/nature06846

[11] Gretarsdottir S, Baas AF, Thorleifsson G, Holm H, den Heijer M, de Vries JP, et al. Genome-wide association study identifies a sequence variant within the DAB2IP gene conferring susceptibility to abdominal aortic aneurysm. Nature Genetics. 2010;**42**:692-697. DOI: 10.1038/ng.622

[12] Koriyama H, Nakagami H, Katsuya T, Sugimoto K, Yamashita H, Takami Y, et al. Identification of evidence suggestive of an association with peripheral arterial disease at the OSBPL10 locus by genome-wide investigation in the Japanese population. Journal of Atherosclerosis and Thrombosis. 2010;**17**:1054-1062

[13] Murabito JM, White CC, Kavousi M, Sun YV, Feitosa MF, Nambi V, et al. Association between chromosome 9p21 variants and the ankle-brachial index identified by a meta-analysis of 21 genome-wide association studies. Circulation. Cardiovascular Genetics. 2012;**5**:100-112. DOI: 10.1161/CIRCGENETICS.111.961292

[14] Kullo IJ, Shameer K, Jouni H, Lesnick TG, Pathak J, Chute CG, et al. The ATXN2-SH2B3 locus is associated with peripheral arterial disease: An electronic medical record-based genome-wide association study. Frontiers in Genetics. 2014;**5**(166). DOI: 10.3389/fgene.2014.00166

[15] Abrantes P, Rosa A, Francisco V, Sousa I, Xavier JM, Oliveira SA. Mitochondrial genome association study with peripheral arterial disease and venous thromboembolism. Atherosclerosis. 2016;**252**:97-105. DOI: 10.1016/j.atherosclerosis.2016.07.920

[16] Resnick HE, Rodriguez B, Havlik R, Ferrucci L, Foley D, Curb JD, et al. Apo E genotype, diabetes, and peripheral arterial disease in older men: The Honolulu Asia-aging study. Genetic Epidemiology. 2000;**19**:52-63. DOI: 10.1002/1098-2272(200007)19:1<52::AID-GEPI4>3.0.CO;2-M

[17] Vazquez F, Rodger M, Carrier M, Le Gal G, Reny JL, Sofi F, et al. Prothrombin G20210A mutation and lower extremity peripheral arterial disease: A systematic review and meta-analysis. European Journal of Vascular and Endovascular Surgery. 2015;**50**:232-240. DOI: 10.1016/j.ejvs.2015.04.033

[18] Bayoglu B, Arslan C, Tel C, Ulutin T, Dirican A, Deser SB, et al. Genetic variants rs1994016 and rs3825807 in ADAMTS7 affect its mRNA expression in atherosclerotic occlusive peripheral arterial disease. Journal of Clinical Laboratory Analysis. 2017. DOI: 10.1002/jcla.22174

[19] Renner W, Koppel H, Brodmann M, Pabst E, Schallmoser K, Toplak H, et al. Factor II G20210A and factor V G1691A gene mutations and peripheral arterial occlusive disease. Thrombosis and Haemostasis. 2000;**83**:20-22

[20] Lee AJ, Fowkes FG, Lowe GD, Connor JM, Rumley A. Fibrinogen, factor VII and PAI-1 genotypes and the risk of coronary and peripheral atherosclerosis: Edinburgh artery study. Thrombosis and Haemostasis. 1999;**81**:553-560

[21] Fowkes FG, Connor JM, Smith FB, Wood J, Donnan PT, Lowe GD. Fibrinogen genotype and risk of peripheral atherosclerosis. Lancet. 1992;**339**:693-696

[22] Sabino A, Fernandes AP, Lima LM, Ribeiro DD, Sousa MO, de Castro Santos ME, et al. Polymorphism in the methylenetetrahydrofolate reductase (C677T) gene and homocysteine levels: A comparison in Brazilian patients with coronary arterial disease, ischemic stroke and peripheral arterial obstructive disease. Journal of Thrombosis and Thrombolysis. 2009;**27**:82-87. DOI: 10.1007/s11239-007-0172-z

[23] Sofi F, Lari B, Rogolino A, Marcucci R, Pratesi G, Dorigo W, et al. Thrombophilic risk factors for symptomatic peripheral arterial disease. Journal of Vascular Surgery. 2005;**41**:255-260. DOI: 10.1016/j.jvs.2004.11.015

[24] Todesco L, Angst C, Litynski P, Loehrer F, Fowler B, Haefeli WE. Methylenetetrahydrofolate reductase polymorphism, plasma homocysteine and age. European Journal of Clinical Investigation. 1999;**29**:1003-1009

[25] Pola R, Flex A, Gaetani E, Flore R, Serricchio M, Pola P. Synergistic effect of −174 G/C polymorphism of the interleukin-6 gene promoter and 469 E/K polymorphism of the intercellular adhesion molecule-1 gene in Italian patients with history of ischemic stroke. Stroke. 2003;**34**:881-885. DOI: 10.1161/01.STR.0000062346.70983.DF

[26] Cesari M, Penninx BW, Newman AB, Kritchevsky SB, Nicklas BJ, Sutton-Tyrrell K, et al. Inflammatory markers and onset of cardiovascular events: Results from the health ABC study. Circulation. 2003;**108**:2317-2322. DOI: 10.1161/01.CIR.0000097109.90783.FC

[27] Renner W, Pabst E, Paulweber B, Malaimare L, Iglseder B, Wascher TC, et al. The angiotensin-converting-enzyme insertion/deletion polymorphism is not a risk factor for peripheral arterial disease. Atherosclerosis. 2002;**165**:175-178

[28] Brevetti G, Schiano V, Chiariello M. Cellular adhesion molecules and peripheral arterial disease. Vascular Medicine. 2006;**11**:39-47. DOI: 10.1191/1358863x06vm645ra

[29] Cassar K, Bachoo P, Ford I, Greaves M, Brittenden J. Platelet activation is increased in peripheral arterial disease. Journal of Vascular Surgery. 2003;**38**:99-103

[30] Fontana P, Gaussem P, Aiach M, Fiessinger JN, Emmerich J, Reny JL. P2Y12 H2 haplotype is associated with peripheral arterial disease: A case-control study. Circulation. 2003;**108**:2971-2973. DOI: 10.1161/01.CIR.0000106904.80795.35

[31] Flex A, Gaetani E, Angelini F, Sabusco A, Chilla C, Straface G, et al. Pro-inflammatory genetic profiles in subjects with peripheral arterial occlusive disease and critical limb ischemia. Journal of Internal Medicine. 2007;**262**:124-130. DOI: 10.1111/j.1365-2796.2007.01791.x

[32] Fatini C, Sticchi E, Sofi F, Said AA, Pratesi G, Pulli R, et al. Multilocus analysis in candidate genes ACE, AGT, and AGTR1 and predisposition to peripheral arterial disease: Role of ACE D/−240T haplotype. Journal of Vascular Surgery. 2009;**50**:1399-1404. DOI: 10.1016/j.jvs.2009.07.075

[33] Wassel CL, Lamina C, Nambi V, Coassin S, Mukamal KJ, Ganesh SK, et al. Genetic determinants of the ankle-brachial index: A meta-analysis of a cardiovascular candidate gene 50K SNP panel in the candidate gene association resource (CARe) consortium. Atherosclerosis. 2012;**222**:138-147. DOI: 10.1016/j.atherosclerosis.2012.01.039

[34] Allis CD, Jenuwein T. The molecular hallmarks of epigenetic control. Nature Reviews Genetics. 2016;**17**:487-500. DOI: 10.1038/nrg.2016.59

[35] Man HS, Yan MS, Lee JJ, Marsden PA. Epigenetic determinants of cardiovascular gene expression: Vascular endothelium. Epigenomics. 2016;**8**:959-979. DOI: 10.2217/epi-2016-0012

[36] Krishna SM, Dear A, Craig JM, Norman PE, Golledge J. The potential role of homocysteine mediated DNA methylation and associated epigenetic changes in abdominal aortic aneurysm formation. Atherosclerosis. 2013;**228**:295-305. DOI: 10.1016/j.atherosclerosis.2013.02.019

[37] Tsaprouni LG, Yang TP, Bell J, Dick KJ, Kanoni S, Nisbet J, et al. Cigarette smoking reduces DNA methylation levels at multiple genomic loci but the effect is partially reversible upon cessation. Epigenetics. 2014;**9**:1382-1396. DOI: 10.4161/15592294.2014.969637

[38] Li T, Cao H, Zhuang J, Wan J, Guan M, Yu B, et al. Identification of miR-130a, miR-27b and miR-210 as serum biomarkers for atherosclerosis obliterans. Clinica Chimica Acta. 2011;**412**:66-70. DOI: 10.1016/j.cca.2010.09.029

[39] Stather PW, Sylvius N, Wild JB, Choke E, Sayers RD, Bown MJ. Differential microRNA expression profiles in peripheral arterial disease. Circulation. Cardiovascular Genetics. 2013;**6**:490-497. DOI: 10.1161/CIRCGENETICS.111.000053

[40] Stather PW, Sylvius N, Sidloff DA, Dattani N, Verissimo A, Wild JB, et al. Identification of microRNAs associated with abdominal aortic aneurysms and peripheral arterial disease. The British Journal of Surgery. 2015;**102**:755-766. DOI: 10.1002/bjs.9802

[41] Pipinos II, Swanson SA, Zhu Z, Nella AA, Weiss DJ, Gutti TL, et al. Chronically ischemic mouse skeletal muscle exhibits myopathy in association with mitochondrial dysfunction and oxidative damage. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 2008;**295**:R290-R296. DOI: 10.1152/ajpregu.90374.2008

[42] Shameer K, Klee EW, Dalenberg AK, Kullo IJ. Whole exome sequencing implicates an INO80D mutation in a syndrome of aortic hypoplasia, premature atherosclerosis, and arterial stiffness. Circulation. Cardiovascular Genetics. 2014;**7**:607-614. DOI: 10.1161/CIRCGENETICS.113.000233

[43] Han P, Hang CT, Yang J, Chang CP. Chromatin remodeling in cardiovascular develop ment and physiology. Circulation Research. 2011;**108**:378-396. DOI: 10.1161/CIRCRESAHA.110.224287

[44] Yamada Y, Ichihara S, Nishida T. Molecular genetics of myocardial infarction. Genomic Medicine. 2008;**2**:7-22. DOI: 10.1007/s11568-008-9025-x

[45] Huang Y, Xu M, Xie L, Wang T, Huang X, Lv X, et al. Obesity and peripheral arterial disease: A Mendelian randomization analysis. Atherosclerosis. 2016;**247**:218-224. DOI: 10.1016/j.atherosclerosis.2015.12.034

[46] Lusis AJ, Mar R, Pajukanta P. Genetics of atherosclerosis. Annual Review of Genomics and Human Genetics. 2004;**5**:189-218. DOI: 10.1146/annurev.genom.5.061903.175930

[47] Patel CJ, Bhattacharya J, Butte AJ. An environment-wide association study (EWAS) on type 2 diabetes mellitus. PLoS One. 2010;**5**:e10746. DOI: 10.1371/journal.pone.0010746