GENOMIC MEDICINE IN CARDIOVASCULAR DISORDERS

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INTRODUCTION

Humans have known for millennia that heredity affects health and disease. But, for most of the medical practitioners; genetics has always been envisioned as an esoteric academic specialty. However, with the completion of Human Genome project on 14th April 2003 and resultant birth of "New Genetics" or Genomic Medicine, genetics is well poised to take the center stage in clinical medicine and we are challenged to find our bearings in a discipline where new operating rules seem to apply.

Genetics is the study of single genes and their effects; while Genomics is the study of functions and interactions of all genes in the genome, including their interactions with environmental factors [1]. Consequently, genomics is envisaged with more broader and ambitious reach than genetics. In the next decade, it is anticipated that Genomic Medicine will exert a profound influence on our understanding and management of human disease. One important area of focus will be cardiovascular diseases, the leading cause of death in men and women in developed and developing world [2]. Although, epidemiological studies and randomized clinical trials have provided compelling evidence that coronary heart disease is largely preventable [3], there is also reason to believe that there is a heritable component to the disease [4]. While major findings in cardiovascular genomics have been few to the date, this review will provide a broad window into how far this field has come and where it is going.

First, we will give a short analysis of monogenic cardiovascular disorders (illnesses in which consistently single gene has been found to be mutated or defective) which are known to us for long time but are relatively uncommon in our setup. We will than discuss the possible role of genomic medicine in more common polygenic / multifactorial cardiovascular disorders (illnesses caused by several genes acting on a single trait, and possibly gene/environment interaction) like Ischemic Heart Disease, Heart Failure, etc. It will be pertinent to mention that, we will restrict ourselves to only genetic aspects of specific cardiovascular illnesses in the scenario of clinical practice, and clinical features of specific diseases will not be discussed.

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MONOGENIC CARDIOVASCULAR DISORDERS

Basic purpose to discuss these illnesses is to highlight the processes by which single gene can cause a disease and thus form the genetic basis of specific diseases.

1. Lipid Disorders

Among these, four monogenic diseases elevate LDL levels through mutant genes with consequent impaired activity of hepatic LDL receptors. These include followings:

a. Familial Hypercholesterolemia (FHC): Primary defect in FHC is deficiency of LDL receptors. To date, more than 600 mutations are documented in the LDLR gene [5] and about 1 in 500 people is heterozygous for at least one such mutation, whereas only one in a million is homozygous at a single locus [4]. Heterozygous produce half the normal number of LDL receptors, leading to an increase in plasma LDL levels by a factor of 2 or 3, whereas LDL levels in those who are homozygous are 6 to 10 times the normal levels [4]. Homozygous persons have severe coronary atherosclerosis and usually die in childhood due to premature CAD.

b. Familial ligand-defective apolipoprotein B-100: Normally LDL binds to APO B 100 which than binds LDL receptor on hepatocytes and remove LDL from plasma. Mutations in APOB100 gene reduce the binding of apolipoprotein B-100 to LDL receptors and slow the clearance of plasma LDL [6]. 1 in 100 people is heterozygous for one of these mutations and lipid profiles as

well as clinical disease is similar to heterozygous FHC.

c. Sitosterolemia: a rare autosomal disorder, results from loss of function mutations in genes encoding two ATP-binding cassette (ABC) transporters, ABC G5 and ABC G8 [7,8], which act in concert to export cholesterol into the intestinal lumen. There is diminishing cholesterol absorption with suppressed hepatic cholesterol clearance and variable elevations in serum cholesterol [7].

d. Autosomal recessive hypercholesterolemia: a variable deficit in LDL receptor activity is seen in patients with mutations in ARH gene leading to moderate elevation in serum cholesterol upto 450mg/dl [4].

2. Hypertrophic Cardiomyopathy (HC)

Hypertrophic cardiomyopathy is transmitted in an autosomal dominant pattern and is considered to be the most common monogenic cardiac disorder [9]. Based on echocardiography, incidence of HC is estimated to be as high as 1 in 500 young adults [10]. Multiple causative mutations in genes encoding for at least 10 different myocardial contractile proteins including cardiac myosin beta heavy chain, cardiac myosin binding protein, cardiac troponin T, cardiac troponin I, alpha tropomyosin, essential and regulatory light chains, and cardiac actin have been identified [11]. Among them mutation in the gene encoding for beta myosin heavy chain were first to be identified [12], and these mutations result in formation of abnormal sarcomere contractile proteins. Although more than 100 disease causing mutations have been identified in patients with familial hypertrophic cardiomyopathy, they may lead to variable clinical outcomes as given below.

a. An Arginine to Glutamine substitution at position 403 (Arg403Gln) and an Arginine to Tryptophan substitution at position 719 (Arg719Trp) affecting beta myosin heavy chain, predispose the patients to sudden death and heart failure [13].

b. A Phenylalanine to cysteine substitution at position 513 (Phe513Cys), a leucine to valine substitution at position 908 (Leu908Val) and a glycine to glutamic acid substitution at position 256 (Gly256Glu), again affecting beta myosin heavy chain, is associated with less severe clinical illness [13].

c. Mutations affecting cardiac myosin binding protein produce late onset HC with a favorable outcome [14].

It is estimated that in addition to sarcomere mutations, numerous other factors like environment, sex and acquired conditions such as IHD or valvular heart disease; determine the pathological features and clinical course of hypertrophic cardiomyopathy [4]. Interestingly, identical sarcomere mutations can cause different hypertrophic changes and clinical outcomes among kindred's, even within the same pedigree [15]. While studies examining polymorphisms in the genes encoding for angiotensin II, aldosterone, and endothelin that may modify the phenotype of HC have not yielded consistent results [16,17,18].

3. X-linked Cardiomyopathy

With the advent of genomics, a family of disorders due to mutations in Dystrophin gene known as Dystrophinopathies has been regrouped [19]. It includes Duchenne's and Becker's muscular dystrophies and newly recognized X-linked cardiomyopathy (XCMP). XCMP is caused by specific mutations in dystrophin gene that lead to the selective loss of dystrophin from cardiac muscle, while dystrophin levels in skeletal muscles remain normal or nearly normal [20].

4. Hypertension and Genes

Hypertension is an established coronary artery disease risk factor and many clinical trials have shown that control of blood pressure reduces the incidence of stroke and myocardial infarction [21]. Although in majority of cases hypertension is multifactorial, few rare mutations may impair renal salt handling, and provide a molecular basis for pathogenesis of hypertension [22]. Some monogenic types of hypertension are discussed below:

a. Pseudohypoaldosteronism Type II (PHA II): It is an autosomal dominant disorder characterized by hypertension, hyperkalemia, increased renal salt reabsorption, and impaired potassium and hydrogen excretion. Two genes causing PHA II are identified; both encode proteins in the WNK family of serine-threonine kinases [23]. These are mutations in

WNK1 on chromosome 12p (intronic deletions) and hWNK4 on chromosome 17 (missense). Immunofluorescence assays have shown that that the proteins localize to the distal nephrons and may serve to increase transcellular chloride conductance in the collecting ducts, leading to salt reabsorption, increased intravascular volume and diminished secretion of potassium and hydrogen ions [4].

b. Glucocorticoid-remediable hypertension: is an autosomal dominant disorder featuring early-onset hypertension with suppressed renin activity and normal or elevated aldosterone. This type of aldosteronism is caused by gene duplication arising from an unequal crossover between two genes that encode aldosterone synthase and 11 B-hydroxylase. [24]. It results in an ectopically expressed protein in adrenal fasciculata with aldosterone synthase activity under the control of corticotrophin rather than angiotensin II [25].

c. Liddle's Syndrome: is an autosomal dominant trait characterized by early-onset hypertension, hypokalemic alkalosis, suppressed renin activity, and low plasma aldosterone levels due to mutations in the genes encoding for Beta or Gamma subunit of epithelial sodium channel [26], with consequent hyperactivity of the channel [27].

d. Hypertension exacerbated by pregnancy: is an uncommon entity, in which, a mutation in the ligand binding domain of the mineralocorticoid receptor results in a conformational change in receptor. Consequently, receptor activation ensues by steroids lacking 21 hydroxyl group. It is hypothesized that increased progesterone levels in pregnancy result in mineralocorticoid like activity through activation of altered mineralocorticoid receptors [4].

5. Hypotension and Genes

Where hypertension is a unanimous risk factor for CAD, we do see patients with persistently low blood pressure with or without symptoms. With the advent of genomics, we may be able to identify some of these cases to be suffering from monogenic hypotensive diseases such as:

a. Aldosterone Synthase and 21 Hydroxylase Deficiencies: It results from loss of function mutations in genes encoding for aldosterone synthase and 21 hydroxylase respectively. Both result in reduced / absent aldosterone levels which lead to impaired renal salt handling and secretion of potassium and hydrogen ions in distal nephrons with consequent reduced intravascular volume and hypotension [28].

b. Pseudohypoaldosteronism Type I: it may be transmitted in autosomal dominant or recessive manner. In autosomal dominant variety, there is loss of function mutations in the mineralocorticoid receptor, with impaired renal salt absorption and condition tends to improve with age and salt replacement. While in autosomal recessive type, loss of function mutation effect the ENaC (epithelial sodium channel) subunits; and shows no improvement with age and generally requires massive salt replacements [4].

c. Gitelman's and Bartter's Syndromes: loss of function mutations in the gene encoding the thiazide-sensitive sodium chloride co-transporter in the distal convoluted tubules cause Gitelman's Syndrome [29]. Patients present in adolescence or early adulthood with neuromuscular signs and symptoms, a lower than normal blood pressure, a low serum magnesium level, and a low urinary calcium level. While Bartter's Syndrome can be produced by a mutation in any of three genes required for normal salt reabsorption in the thick ascending loop of Henle [30]. It can be distinguished from Gitelman's Syndrome as it features increased urinary calcium levels and normal or reduced magnesium levels [30]. Due to avid salt loss both conditions are associated with activation of renin angiotensin, subsequent activation of mineralocorticoid receptor and increased ENaC activity; thus preserving salt homeostasis to some extent [4].

6. Cardiac Tachyarrhythmias

We all know that cardiac tachyarrhythmias are an important cause of sudden death. In this regard, arrhythmia susceptibility genes have been identified and thus provide an insight into the molecular basis of lethal and non lethal tachyarrhythmias. Three monogenic disorders with increased susceptibility to arrhythmias are given below:

a. Long QT Syndrome (LQTS): is a familial disorder characterized by abnormally prolonged ventricular repolarization (QT interval on surface ECG) and risk of malignant ventricular tachycardias occurring usually (but not always) in settings of high adrenergic states like physical and emotional stress. Based upon identification of mutant genes and their location it is further sub typed as below [31]:

Subtype	Mutant gene/ion channel	Chromosome No.
LQT 1	KvLQT 1 (l ks)	11
LQT 2	HERG (I kr)	7
LQT 3	SCN5A (I Na)	3
LQT 4	UNKNOWN	4
LQT 5	KCNE 1 (mink)(I ks)	21
LQT 6	KCNE 2 (Mirp)(I ks)	21
LQT 7	KCNJ 2 (I ks)	17

As regards the underlying pathogenic mechanisms, the SCN5A gene normally encodes alpha subunits that form the sodium channels responsible for initiation of cardiac action potential [32]. Now, gain of function mutation of SCN5A gene like variant allele Y1102, accelerates sodium channel activation and channel reopens during plateau phase of action potential; thus increases the likelihood of abnormal repolarization and arrhythmias [33]. Similarly, HERG gene encodes alpha subunits that assemble with beta subunits of mink-related peptide 1 (MiRP-1) to form cardiac Ikr potassium channels, which facilitate repolarizing potassium current [34]. In turn, KVLQT1 alpha subunits assemble with mink beta subunits to form cardiac Iks potassium channels, which facilitate second repolarizing potassium current [35]. These channels terminate the plateau phase of action potential, causing myocyte repolarization. KVLQT, HERG, mink and MiRP1 mutations result in a loss of function or missense in the potassium channel that leads to further subtypes of long QT syndrome [31].

b. Idiopathic or Familial Ventricular Fibrillation: whereas gain of function mutation in SCN5A lead to Long QT syndrome, loss of function mutation in same gene leads to idiopathic or familial type of VF. It is proposed that this mutation results in reduction in total number of functional sodium channels with expression of heterogeneous group of sodium channels, which may shorten the action potential and lead to VF [36].

c. Catecholamine Induced Ventricular Tachycardia: is associated with missense mutation in RyR2 which normally encodes for ryanodine-receptor calcium release channel required for excitation contraction coupling. The mutation probably results in stress-induced calcium overload in cardiac myocytes with consequent VT [36].

POLYGENIC / MULTI FACTORIAL CARDIOVASCULAR TRAITS

Although many single genes have been identified as the basis of monogenic cardiovascular disorders, fewer genes underlying complex cardiovascular traits have been identified [37]. Presence of multiple risk factors, gene-gene and gene-environment interactions, genetic heterogeneity, low penetrance, and an absence of rough estimates of the number of genes that influence a single trait; all complicate genetic analysis and study designs [4]. Current research on complex cardiovascular traits focuses on the identification of genetic variations and varied gene expressions that enhance the susceptibility to given conditions [37]. Before describing the genomics of common complex CVD's, it may be relevant to define the phenomenon of gene polymorphism and gene expression profiling; the main ways to identify genetic associations in polygenic CVD's.

Gene Polymorphism

Human genome consists of about 3 billion base pairs and two unrelated persons are believed to share 99.9% of their DNA sequences [38]. However, there are natural variations in a gene, DNA sequence, protein, or chromosome that have no adverse effect on the individual called Polymorphisms and occur with fairly high frequency in the general population. While single nucleotide polymorphism (SNP's) are sites in human genome where individuals differ in their DNA sequence, often by a single base [39]. Scientists believe that human genome contains approximately 10 million SNP's, and study of these SNP's may be relevant to specific genotypic and phenotypic variations relevant to the health and disease [1]. In this regard, association studies (studies of affected persons and control subjects) provide a powerful approach to identify SNP's

underlying complex CVD's and than narrowing a candidate interval identified by linkage analysis (testing DNA sequence polymorphism that are near or within a gene of interest to track within a family the inheritance of a disease-causing mutation in a given gene) [40]. Improved genotyping (testing that reveals the specific alleles [one version of a gene at a given locus] inherited by an individual) techniques, such as genome wide scanning of SNP's and mapping of SNP's, identifying common haplotypes (collection of SNP's that are inherited in blocks) in the human genome, are facilitating association studies of loci spanning the entire genome [39]. Then by use of high-throughput genomic techniques like DNA microarray, genetic variations can be investigated in a large number of candidate genes associated with different CVD's [4]. It is hoped that understanding of genomic variation by gene polymorphism may improve the prediction of disease susceptibility, prognosis and response to drug therapy [39].

Polymorphism association studies compare the prevalence of a genetic marker in unrelated people with a given disease to the prevalence in a control population. In case of CVD's, these studies should be interpreted with caution when biologic plausibility has not been determined or is not known. SNP's in linkage disequilibrium (the non random association in a population of alleles at nearby loci) may be functionally important or alternatively, the polymorphism may just be a marker for another, yet to be identified, disease-causing sequence variation [4]. It is pertinent to highlight that because of racial and ethnic differences in genetic polymorphisms, it is important to construct a data base of polymorphisms related to CVD's in each racial and ethnic group [39].

Gene Expression Profiling

Functional genomics or study of gene functions by means of parallel measurements of expression within control and experimental genomes are useful tools to establish molecular diagnoses, dissect the pathophysiological features of a disease and predict patient's response to the therapy [41]. It involves the use of DNA microarrays and serial analysis of gene expression. DNA microarrays are miniaturized, systematic immobilization of nucleic acid fragments procured from individual genes on a solid support, which by specific hybridization; enable simultaneous analysis of thousands of genes in parallel [42]. Segments of DNA that serve as probes for detection are arranged regularly on nylon or a glass support, which forms the so called 'gene chip' or microarray [43]. Hybridizing these arrays with labeled nucleic acids from tissue samples allows quantitative measurement and comparison of genetic information [44]. The microarray technology has been useful not only in gene expression profiling but also for genotyping, mutational and gene resequencing analysis [45].

Now after this brief introduction about complexities of genomics in common polygenic CVD's, we will describe each disorder separately.

1. Premature Coronary Artery Disease (CAD) and Genes

In 1990's, Gene Quest Study was started to search for candidate genes associated with premature CAD (defined as CAD in men <45years old and women <50 years old). In this case-control study, initially 62 genes and then 111 candidate genes in patients and their siblings with premature CAD are investigated. The study identified three variants in the genes encoding for thrombospondin-4 (THBS-4), thrombospondin-2, and thrombospondin-1; to be significantly associated with premature CAD [46]. In 2004, they have noted A387P polymorphism in THBS-4 to be the strongest association along with plasminogen activator inhibitor-2 polymorphism as independent predictor for premature CAD [47]

As an extension of original Gene Quest project, Gene Quest 1A Study was started to use single large families with premature CAD/MI to map and find genes for premature CAD. A specific marker, D15S120 on chromosome 15q26 has been associated with mutant MEF2A (Myocyte Enhancer Factor-2A) and was found to be associated with familial premature CAD/MI [48]. MEF2A protein is a transcription factor, normally known to function in vascular development and angiogenesis [48].

2. Ischemic Heart Disease/MI and Genes

Yamada and colleagues examined the prevalence of 112 polmorphisms in 71 candidate genes in patients with myocardial infarction and

control patients in Japan [49]. The analysis identified one significant association in men – a cytosine to thymine polymorphism at nucleotide 1019 in the connexin 37 gene. While in women, 4G – 668/5G in the plasminogen activator inhibitor type 1 gene and 5A – 1171/6A in the stromelysin-1 gene; were significant SNP's associated with MI in this population [49]. In a recent analysis of polymorphisms in 40 candidate genes, McCarthy and associates have noted significant association for coronary heart disease in 10: ACE, APOE, F7, FGB, GP1BA, IL1RN, LRP1, MTHFR, SELP, and THPO [47].

3. Susceptibility to Atherosclerosis/ Thrombosis and Genomics

Some genetic influences that may increase individual susceptibility to develop atherosclerosis or thrombosis and thus CAD, are as under:

a. A common variant in the factor V gene, one encoding the substitution of glutamine for arginine at position 506 (Arg506Gln), prevents the degradation of factor V and promotes clot formation. This substitution also known as factor V Leiden (basically a monogenic CVD), has been observed in 20 – 50% of patients with venous thromboembolic disease and also increases the risk of myocardial infarction and stroke in men [50].

b. In a recent meta analysis, individuals homozygous for the polymorphisms at Asp298 and intron (a region of a gene that does not code for a protein) 4a alleles of endothelial nitrous oxide synthase (eNOS) are at moderately increased risk of IHD [50]. It is proposed that common genetic variations in the eNOS gene contribute to atherosclerosis susceptibility, presumably by effects on endothelial NO availability [51].

c. Lipoprotein (a) is an LDL like particle in which an apolipoprotein (a) moiety is linked via a disulfide bond to apo B-100 [52]. Concentration of Lp(a) are largely under genetic control and vary substantially between individuals depending on size of the apo(a) isoform present; conversely, Lp(a) levels vary little with diet or exercise [53]. Raised Lp(a) levels have been proposed as significant predictors of atherosclerosis and CAD [54]. The wide range of Lp(a) in plasma within a population is due in large p[art to a variable number of plasminogen like kringle IV repeats, and an inverse correlation between the number of these repeats in apo(a) gene and Lp(a) plasma concentration exists [55]. Although biological function of Lp(a) is still unclear, its phylogenetic role may have been to respond to tissue injury and vascular lesion and to promote wound healing [54]. Its most important putative role in atherothrombosis may be to inhibit clot fibrinolysis at sites of tissue injury and is thought to compete with plasminogen for binding to fibrinogen and fibrin [56].

d. Hyperhomocysteinemia: It has been postulated that mild to moderate elevations of homocysteine predispose to atherosclerosis [54]. Mechanistic studies have shown that homocysteine may induce vascular damage by promoting platelet activation, oxidative stress, endotheleial dysfunction, hypercoagualability, and vascular smooth muscle cell proliferation [57, 58]. In a recent meta analysis of MTHFR 677 C—T polymorphism (a mutation in gene encoding for methylenetetrahydrofolate reductase – the enzyme responsible for metabolism of homocysteine) confirmed modest but statistically significant increases in risk of IHD in homozygotes for the mutant allele TT [59,60].

4. Heart Failure and Genes

Sustained cardiac adrenergic stimulation has been implicated in the development and progression of heart failure [61]; with substantial variations among persons in the expression and function of adrenergic receptors, the development and progression of heart failure, and the response to beta-blocker therapy [62]. In this regard, Small and colleagues described an association between two polymorphisms in adrenergic receptor genes and the risk of congestive heart failure in black Americans [63]. The coding polymorphism of the gene for alpha 2c receptors – the deletion of four consecutive amino acids (Del322-325); results in loss of normal synaptic autoinhibitory feedback with consequent enhanced presynaptic release of nor epinephrine [63]. While another polymorphism at Beta1 adrenergic receptors –

B1Arg389; may increase the sensitivity of cardiomyocytes to nor epinephrine [63]. It was elucidated that, patients who are homozygous for both variants had markedly increased incidence of heart failure. Genotyping at these two loci may be a useful approach for identification of persons at risk for heart failure or its progression, who may be candidates for early preventive measures [63].

5. Genomics and Congenital Heart Defects

In last decade, the role of genes, their critical timing of expression and understanding of important downstream pathways for optimizing normal development and control of the right left asymmetry have highlighted the importance of field of genomics in congenital heart defects (CHD's) [64]. Through genetic linkage analysis of pedigrees, so far one gene – NKX2-5 has been noted to be associated with nonsyndromic CHD's [65]. While Garg and colleagues have identified two mutations in GATA4, a transcription factor essential for heart formation, to be associated with syndromic cardiac septal defects [65]. These include G296S – a missense mutation (substitution of a single DNA base that results in a codon [a three base sequence of DNA or RNA that specifies a single aminoacid] that specifies an alternative amino acid), resulting in GATA4 with diminished DNA binding affinity and transcriptional activity. While E359del – a frame shift mutation (the addition or deletion of a number of DNA bases that is not a multiple of three, thus causing a shift in the reading frame of the gene. This shift leads to a change in the reading frame of all parts of the gene that are downstream from the mutation, often leading to a premature stop codon and ultimately, to a truncated protein) leads to formation of transcriptionally inactive GATA4 [65]. It is further implicated that, these GATA4 mutations may also abrogate a physical interaction between GATA4 and TBX5, a T-box protein responsible for syndromic CHD's [65].

6. Instent Re-stenosis and Genomics

Zohlnhofer and colleagues identified clusters of differentially expressed genes from coronary artery intima and peripheral blood cells from patients with restenosis, and found up regulation of genes with functions in cell proliferation, the synthesis of extra cellular matrix, cell adhesion, and inflammatory responses [66]. In another study Renin Angiotensin Aldosterone System (RAAS) gene polymorphism was noted to be a risk factor for instent restenosis [67]; while polymorphisms at D/D variant of ACE gene, Platelet glycoprotein IIIaPIA/A2 gene and Interleukin I receptor antagonist gene have also been found to increase the risk of instent restenosis [68].

GOOD GENOMICS IN CAD

So far we have mentioned various bad genes and their effects in coronary artery disease. But researchers have described a mutation (Argenine to Cysteine) in Apolipoprotein A1 (a protein that is packaged with cholesterol in high density lipoprotein) in residents of a town Limone sul Garde in Milan – Italy, that is associated with very low levels of HDL with amazingly low incidence of CAD and longevity [69, 70]. The so called **"**Milano**"** lipoprotein or mutant HDL is hypothesized to possess antioxidant properties [71] and is exceptionally efficient at removing plaque from arteries [69]. A recombinant Apo A1 has already been used in patients with CAD with beneficial effects [69] while a search for ways and means to induce such mutations in people with CAD is underway.

PHARMACOGENOMICS IN CARDIOLOGY

Use of genome-wide approaches to determine the role of DNA variations in individual responses to drugs is called Pharmacogenomics [72]. Genetic polymorphisms have been shown to have clinical implications in drug metabolism, its transport and even at drug receptor/target levels [73]. Some examples of genetic polymorphism with effects on efficacy of cardiovascular drugs are given below:

a. ABCB1/MDR1 gene and Digoxin: a synonymous single nucleotide polymorphism (SNP) (a SNP that does not alter the amino acid encoded) of ABCB1/MDR1 gene in exon (a region of the gene that encodes for a protein) 26 with mutant allele – C3435T, has been associated with higher oral bioavailability of digoxin [74] and atrial arrhythmias and heart failure [75].
b. ACE gene and angiotensin converting enzyme inhibitors: Insertion / Deletion (I/D) polymorphism of ACE gene has been implicated with therapeutic effects like

reduction in blood pressure [76], improvement in heart failure [77], reduction in left ventricular mass [78], improvement in endothelial dependent vasodilatation [79], renoprotective effects in chronic proteinuric nephropathies [80], and decreased LDL with regression of atherosclerosis in response to use of statins especially fluvastatin [81].

c. ADRB2 gene and response to B2 adrenergic agonists: Dishy and colleagues have noted two common polymorphisms of the B2 adrenergic receptors; an arginine to glycine substitution at codon 16 (Gly16) and a glycine to glutamine substitution at codon 27 (Glu27) are associated with increased agonist associated desensitization and increased resistance to desensitization respectively [82]. These polymorphisms translate clinically to desensitization after continuous (>90 min) isoproterenol infusion with reduced venodilatation in patients with Arg at ADRB2 codon 16 as compared to no effect on venodilatation in patients with Gly at same location [73].

d. APOE, CETP (cholesterol ester transfer protein), and Stromelysin-1 genes and statins: Both phenotypic and genotypic analyses of the APOE polymorphism have shown an association between APOE genotype and the response to lipid lowering drugs [83]. In most studies, greatest diminution in LDL levels with various statins was noted with APOE2 allele followed by with APOE3 and than APOE4 [84]; and in some studies even regression of atherosclerotic lesions with statin therapy is associated with this genotype [85]. While Kuivenhoven and colleagues have identified CETP gene to be specifically associated with regression of atherosclerotic lesions after use of Parvastatin [86]. In another study, Stromelysin-1 was noted to be implicated in reduction of cardiovascular events and reduction in risk of repeated angioplasty [87].

e. Ion Channel genes for LQTS. As already mentioned in cardiac tachyarrhythmias in monogenic CVD's; mutant cardiac ion channel genes like HERG, Mink, MiRP1, and KvLQTS1 are associated with different forms of LQTS. Presence of these genes increase the propensity to develop ventricular tacyarrhthmias especially Torsade de pointes after use of Erythromycin, Terfaenadine, Cisparide, Calrithromycin, Quinidine, and Trimethoprim – Sulfamethoxazole [88,89].

f. Wafarin and Cytochrome P-450 (CYP) variants: use of pharmacogenetic testing may help in tailoring the dose of some drugs like Warfarin. It is found that patients homozygous for the 2 and 3 alleles of CYP – 2C9 are more likely to have enhanced drug effect with frequent bleeding complications and unstable anticoagulation [90].

CONCLUSION

Genomic medicine in cardiovascular diseases is a rapidly evolving field. Expectations are high for the potential of cardiovascular genomics to lead to major advances in our understanding of normal cardiovascular functioning and molecular basis of cardiovascular disease pathogenesis, of strategies for CVD's prediction, to envisage varied genetic gravities of clinical presentations and in elucidation of drug response and development. However, the real challenge remains the analysis of more common cardiovascular traits with clinically meaningful outcomes.

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