Cardiovascular Disease and Heredity:

Possibilities for Prevention and Management with Genetics

Abstract

Cardiovascular disease (CVD) is one of the world's leading causes of illness and death. Researchers estimate that its prevalence will continue to rise over the next few decades. Until now, public prevention strategies have relied predominately on managing environmental factors that contribute to CVD, such as obesity, smoking and lack of exercise. Recently, the understanding of the role of genetics in CVD development has become much more important as researchers have begun to link genetics with the onset of disease and response to therapy. This paper seeks to examine how genes can predispose individuals to CVD and how this knowledge might be applied to more comprehensive preventative strategies in the future. In addition, the paper explores possibilities for genetics in CVD treatment, particularly through the use of pharmacogenetics, pharmacogenomics and gene therapy.

Nature and Prevalence of CVD

In 2001, cardiovascular diseases (CVD) caused about one-third of all mortalities, with about 85% of these deaths occurring in low to middle income countries. The World Health Report of 2002 estimates that it will become the major cause of death in high-income countries [1]. The most prevalent CVDs include ischaemic heart disease (heart attack), cerebrovascular disease (stroke), hypertension, inflammatory heart disease and rheumatic heart disease in that order of prevalence [1]. Together these five major CVDs are linked to over 16 million deaths annually, with heart attacks alone affecting 12.7 % of the global population, followed by stroke, which affects 9.6% of the global population. Researchers estimate that the number of annual deaths and mortality rate will continue to rise in the coming years, especially in high-income countries.

It is important to recognise that the numbers of CVD associated deaths per year are much higher in certain regions than others. The WHO has subdivided the six WHO geographic regions into sub-regions according to infant and adult mortality rates. Deaths due to CVD in the very low child and very low adult mortality regions in the Americas were 1,106,000 per year compared to 1,760,000 deaths in the corresponding regions in Europe [1]. Conversely, deaths due to CVD in the high child and very high adult mortality regions in Africa were 503,000 per year [1]. These regional disproportions in deaths due to CVD may be intertwined with socio-economic inequities among these regions in addition to other possible environmental and genetic factors inherent in their respective populations. In both high income and low to middle income countries, the economically impoverished suffer a much higher mortality rate than the wealthy. The socio-economic factor can be better illustrated at the country-level. In 1999, over 78% of total CVD mortality was assumed by low to middle income countries. This may be a result of inadequate treatment and risk assessment facilities, since low-to-middle income countries tend to have less sophisticated technology for treatment and fewer clinical assessment services available to individuals.

In addition to regional and socio-economic disparities, there are also differences in the prevalence and incidence of CVD according to gender as shown with the following table from the World Health Report, 2002:

Type of CVD	Male		Female	
	(000)	%	(000)	%

Rheumatic heart disease	140	0.5	197	0.7
Hypertensive heart disease	397	1.3	477	1.8
Ischaemic heart disease	3756	12.7	3425	12.7
Cerebrovascular disease	2499	8.4	2956	11.0
Inflammatory heart disease	192	0.6	183	0.7

With the exception of ischaemic heart disease (heart attack), a higher proportion of women than men appear to be affected by the major CVDs. Factors contributing to these differences may be environmental, genetic or in the inherent biological and anatomical differences between men and women [2].

Although it is known that the risk for CVD increases at a faster rate with age in women than men, the reasons are poorly understood. A study at Memorial Hospital of Rhode Island found that women are more likely to participate in CVD research projects than men and that women seem to be more receptive to health advice regarding risk factors and generally show more effort in trying to adopt a healthier lifestyle than men . On the other hand, it was noted an obvious lack of women' representation in clinical research studies and as a consequence, the optimal dosages of medication have largely been adjusted for men and may not necessarily be appropriate dosages for women. Clearly, more research in the area investigating gender-linked disparities is needed to facilitate a better comprehension of the general occurrence of CVD.

Role of Genetics in CVD Development

Direct Genetic Predispositions

A great deal of attention has been given to the environmental causes leading to CVD development. In fact, most risk factor assessments presently take into account only an individual's lifestyle habits (i.e. diet, smoking, or exercise), since CVD is often associated with diabetes, obesity, and other conditions relating to lifestyle. With growing evidence that CVDs have a sizable hereditary component, more emphasis needs to be given to genetic predisposition as a risk factor to achieve a better understanding of the disease development. Genetic predispositions are a result of gene mutations, which alter the biological function expressed by the original gene(s) and increase an individual's risk for a disease. These mutations are more commonly known as polymorphisms. Several polymorphism and linkage markers have already been identified as being directly correlated to the onset of CVDs and more continue to be located by scientists everyday.

A review article by the Hypertension and Rehabilitation Unit at the University of Leuven in Belgium discusses the key polymorphisms that are being looked at as major players in the onset of CVD [3]. Current research has been dominated with genetic differences involving the renin-angiotensin system, which are believed to be at fault for the development of CVD. The renin-angiotensin system monitors blood flow, blood pressure and basic cardiovascular activity. In particular, the M235T polymorphism of the angiotensinogen gene is linked to hypertension [3]. Furthermore, the A1166C polymorphism of the angiotensin II type 1 receptor gene is probably correlated with hypertension and through an epistatic interaction with the D/I polymorphism of the angiotensin-converting enzyme gene possibly also with coronary heart disease [3]. Several other projects are simultaneously looking into other renin-angiotensin mutations, involving random insertion and deletions of gene segments and promoter mutations.

A team at the Hospital de Criancas Maria Pia in Portugal studied the issue of genetic susceptibility in pediatric stroke [4]. Of the 21 children that the team surveyed, it found that 14.3% of the children had a mutation on the Factor V Leiden gene and 9.5% had a mutation on the Factor II G20210A gene. It was concluded that these two genes did contribute to the development of disease and that the condition was also hereditary.

A study at the University of Texas in the U.S. looked at 338 Caucasian and 265 African American individuals from families with a history of hypertension and stroke and performed genetic screening [5]. Their data showed that chromosome 13 carries polymorphisms for hypertension and stroke in the Caucasian participants while chromosome 19 carries such polymorphisms in the African American participants.

Indirect Genetic Predispositions

In addition to polymorphisms that directly increase the risk of CVD onset, there are numerous genes that indirectly increase risk of CVD development. These indirect predispositions are sometimes in the form of genes that predispose unhealthy behaviour, such as alcohol or tobacco consumption--behaviours conducive to CVD development [6].

Researchers have recently been looking at a gene, which predisposes an individual to a smoking habit. The correlation between genetics and the tendency to consume tobacco was shown [7]. Predisposed individuals have difficult of a time in quitting their smoking habit and tend to be long-time smokers. At the same time it was found polymorphisms on genes involved in nicotine metabolism and coding for receptors [8]. These polymorphisms are believed to contribute to the dependence. This is strong evidence that certain genes predispose individuals to certain psychological and physical tendencies that may indirectly contribute to CVD development.

Genes can also indirectly predispose an individual to CVD via polymorphisms that predispose an individual to another disease. Diabetes, for example, significantly increases an individual's risk for CVD due to its impact on the kidney, blood vessels and renin-angiotensin system. Diabetes, itself, is known to be a disease in which genetic predisposition has been largely recognized. Recently, researchers from the University of Mississippi Medical Center found that iron overload syndromes are common and often inherited for diabetes mellitus in descendents of European and African populations [9]. Excessive iron storage is a factor causal to diabetes mellitus and diabetes mellitus is a major known risk factor of cardiovascular disease.

A 2003 study by the King's and St Thomas's School of Medicine in London conducted a study to see if an innate immunity marker could be used to determine the onset of CVD in Type 2 diabetes patients [10]. The team followed 128 patients with Type 2 diabetes for a period of 12.8 years. Forty three percent (43%) of the original participants had died after the 12.8 years, with CVD being the cause of death for 71.4% of these individuals of which, 62.5% was attributed directly to coronary heart disease [10]. It was concluded that because the innate immunity marker gave a very strong predication of a person's development of Type 2 diabetes, it could also be a predictor development of CVD, as the two diseases are linked.

Some genes have been found to have mutual influence in the onset of both type 2 diabetes and CVD. The research team at the Internal Medicine Service of Tarragona, Spain looked at patients with combinations of coronary heart disease (CHD) and Type 2 diabetes and compared them to respective controls. The team found that among patients with both CHD and Type 2 diabetes, there was a notably higher prevalence of polymorphism on the TNF-alpha promoter, than among patients with just isolated cases of CHD or type 2 diabetes [11]. This leads researchers to believe that the polymorphism affects CHD development in patients with Type 2 diabetes and this could be a good indicator of CHD for diabetic patients in the future [11].

High blood pressure or hypertension is a major risk factor of CVD. While several monogenic forms of hypertension are now well dissected [12], as of yet, researchers have not been able to isolate gene(s) of more frequent polygenic (essential) hypertension that contributes significantly to blood pressure elevation although many candidate genes appear to be contributing factors. A recent review article published in the by the University of Melbourne that evaluated the search for genes associated with blood pressure found

that rather than a single gene, many genes contribute to high blood pressure, without any single gene bearing substantial effect on its own [13]. These genes are distributed haphazardly and therefore are difficult to trace. At the population survey of White European families, which used positional cloning, a technique that involves finding position and then function of the gene [14], the team studied 2010 sibling pairs from 1599 families with a history of severe hypertension and found that there is there a principle locus on chromosome 6q and three other loci on chromosomes 2q, 5q and 9q that demonstrate genome-wide significance for hypertension.

Despite tremendous efforts, few major genes involved in the susceptibility for complex disorders of CVD have been identified. Data collected from the French Canadian founder population suggest a genetic link between obesity and early onset ($\leq$ 55 years) hypertension and that hypertension in lean and obese individuals may represent, at least in part, separate genetic entities [15,16]. Furthermore, genes that mediate the response of blood pressure to environmental factors, such as stress and diet, are significant determinants of the hypertensive phenotype [17]. A number of other hypertension-related phenotypes, such as left ventricular hypertrophy, insulin resistance and dyslipidemia are not consistently present in all hypertensive individuals [16]. One explanation is that these disorders are a result of interactions between genes and environment and, under such conditions it may be difficult to measure the true genetic effect without accounting for these interactions [18]. Clearly further research is warranted in this area that may lead to new techniques to improve the management of CVD in the future.

While a great deal of research has been devoted towards investigating negative genetic predispositions for CVD, some genes may reduce an individual's risk of developing CVD. A previous report by the WHO Human Genetics Program highlighted a number of genes that elevate high density lipoprotein (HDL), higher levels of which are known to decrease a person's chances of acquiring CVD [19]. These genes affect hepatic lipase, ApoAI-CII-AIV cluster, cholesterol ester transfer protein and lipoprotein lipase. Similarly, McGill University Health Centre-Montreal Children's Hospital showed that a variant in exon **6**-R239Q, which is involved in the metabolism of homocystine, may actually decrease a person's risk of coronary artery disease (CAD) [20]. The team concluded that the relationship of this variant to CAD as well as other homocysteine-dependent disorders warrants additional investigation.

Understanding the genetics behind the onset and development of CVD is a critical part of the prevention and management of CVD. While genetics may put an individual at risk for disease, environmental factors may decrease or increase a person's chances of developing the disease. A recent study on the implications of polymorphisms of the angiotensin-converting enzyme (ACE) gene on ischemic cerebrovascular disease was conducted at Wonkwang University in South Korea [21]. The team studied the influences of the polymorphism in smoking and non-smoking patients. Tobacco is known to be a major cause of all vascular diseases because it induces blood clotting and also induces constriction of blood vessel. The research found that the polymorphism of the ACE gene was only a risk factor in individuals who smoked and did not appear to be a risk factor for individuals who do not smoke [21]. This information could conceivably discourage many individuals with the ACE polymorphism from smoking, especially if they realize that they are at an elevated risk of developing a CVD.

Genetic factors underlying disease appear to differ between male and female patients [22]. This appears to result at least in part from different physiological effects exerted by sex hormones such that polymorphisms in susceptibility genes may have physiological relevance only in males or females. As an example, there is a 2:1 prevalence of coronary artery disease in male over female patients in younger age groups, but this difference dissipates with increasing age [22]. Moreover, sex differences exist in the clinical manifestations of CAD. Corollary risk factors, such as diabetes and blood pressure, differ dramatically in their impact on CAD between males and females and there is some evidence that genetic variations of some susceptibility genes have sex specific effects [22].

Role of Genetics in CVD Prevention

Primary prevention of CVD includes modification of the so called "environmental risk factors" including tobacco smoke, physical inactivity, obesity and high blood pressure. Most population based CVD prevention and management programs have used primary prevention methods, to encourage certain behaviours while discouraging others through legislation and public campaigns and as such, focus on the encouragement of physical activity, weight loss and smoking cessation. Although this has proven to be a relatively inexpensive approach, a quality important in low to middle income countries, it single emphasis on the environmental factors and lifestyles inherent in a region. The shortcoming of this strategy is that precious resources being allocated to all people, instead of being geared towards select individuals who are at increased risk of developing CVD. Optimised prevention strategies include secondary preventive strategies, which use population screening, individual clinical assessments and aggressive therapy to control blood pressure, high lipids and diabetes in addition to primary prevention strategies. While this method is somewhat more effective, it is often poorly applied particularly in low to middle-income countries that have few resources to sponsor this kind of health care. In the future, comprehensive risk assessment that acknowledges the genetic component as well as the impact of interactions between genes and the environment on outcomes may further optimise population based preventative strategies.

Genetic Testing

Certain individuals are at a higher risk for CVD development as a direct result of their genetic makeup. This genetic "predisposition" puts the individual at a higher risk of disease regardless of environmental factors or healthy lifestyle choices. This type of direct genetic risk usually involves only one gene (monogenic), examples of which include familial hypercholesterolaemia and familial hypertrophic cardiomyopathy or glucocorticoid suppressible hypertension. On the other hand, most CVD is caused by multiple gene variants and, by chance and selection, some individuals and geoethnic groups have more of these variations and others less. Furthermore, interactions between these gene variants and different environmental conditions will produce different outcomes making it difficult to predict how CVD will be expressed in individuals with polygenic variants.

Despite the availability of some genetic tests for individuals with a history of cardiovascular problems, there is still a great degree of uncertainty as to outcome, largely because many susceptibility genes and interactions between genes and the environment have yet to be identified [18]. Furthermore, tests that are currently available are usually found only in the high-income countries and are too costly at the present time to implement globally. An improved understanding of the role of genes and interactions between genes and the environment in CVD will facilitate the creation of more accurate genetic tests and technologies that can be used globally. Similarly, genetic tests which will predict effectiveness and inoquity of antihypertensive medications, while of a tremendous socio-economical interest, are still far ahead in the future.

Population Screening

Classical environmental risk factors combined with blood tests for the ratio of high to low density lipoprotein are highly predictive of CVD outcome. To be useful, genetic screening must provide information that cannot be obtained through risk factors alone and, when coupled with current screening methods, must significantly increase predictive power. Population genetic screening has the potential to determine the genetic characteristics (such as disease alleles prevalence) that are unique to a given particular population. Results can then be used to apply appropriate prevention and treatment strategies that cater to the genetic and environmental dynamics of that specific group of people. Population genetic

screening might also help identify the differences in genetic and environmental susceptibilities between populations that contribute to the disparity in disease prevalence.

Unfortunately, population screening for common, polygenic diseases is not practical at this stage, because genetic testing is still highly uncertain and cannot accurately predict an individual's risk for disease and will potentially even in future remain of probabilistic nature. Furthermore, many countries do not have the resources required to cover the cost of genetic screening let alone screen their respective populations for classical risk factors. When genetic testing is able to more accurately predict risk factors and lower costs, population screening could become a valuable investment for the prevention and management of CVD. Identification of simple phenotypic markers that are highly correlated with genetic predisposition to CVD for populations in a given area under distinct environmental conditions has the potential to significantly reduce costs of implementing population genetic screening strategies in the future. Such advancements would mark a big step in the effort to effectively prevent CVD.

Role of Genetics in CVD Treatment

Sources of Genetic Variability in Treatment Response

Not all patients respond in the same way to treatment. For example, despite appropriate therapy and having achieved target blood pressure, many hypertensive patients will still develop acute myocardial infarction or stroke and far too many appropriately treated heart failure patients still die. Similarly, not all patients respond to behaviour modification in the same way. For example, the standard suggestion for hypertensive patients is to exercise between 20-60 minutes 3 to 5 times per week and that such exercise should lower blood pressure [23]. A clinical Exercise Physiology Laboratory in Indiana University found that exercise alone does not alleviate hypertension in all individuals [23]. The scientific speculation is that genetic variations cause some patients not to respond while allowing others to respond.

Over 50 years ago the recognition of inheritance as an important factor in drug response led to the birth of "pharmacogenetics" [24]. Pharmacogenetics and pharmacogenomics are terms that we see more and more often in the scientific literature and the lay press, however, there is some confusion as to what these terms mean. Definitions that are consistent with the distinctions between genetics and genomics describe pharmacogenetics as the study of variability in a single gene to variable drug response and pharmacogenomics the study of multiple genes, or the entire genome, to variability in drug response [25]. Whereas most early pharmacogenetic research involved drug metabolism, rapid changes in genomic science resulted in the evolution of pharmacogenetics into pharmacogenomics [24].

According to a recent review article, there are a total of 17 families of drugs that are currently used to treat the heterogeneous group of CVDs and 5 sources of genetic variability in response to such medications [26]. These include the genetics of pharmacokinetics, which governs how the body absorbs, distributes, metabolises and excretes drugs from the body; the genetics of pharmacodynamics, which dictates the biochemical and physiologic effects of drugs according to their mechanisms of action within tissue and cellular targets; the genetics that govern metabolic deviations linked to a defined pathology or disease and its corresponding drug therapies; the genetics of physiologic regulation, which dictates how a drug will function according to ethnicity, age and gender; and, how genes and environmental-genetic interactions affect how an individual will respond to a drug [26].

There are known polymorphisms that impact the pharmacokinetics of medications and render an individual unable to process a drug as a normal person would. These polymorphisms can either cause enzymes to lose function and under-metabolise or, alternatively, effect how drug transporter systems affect the absorption, distribution and elimination of drugs [26]. There are data that between 5 and 20 percent of patients have polymorphisms resulting in insufficient metabolism of a drug and about 1 out of every 15 admissions to the

hospital are a result of an unexpected drug response [27]. Furthermore, sometimes these mutations in the body's biological system can be deadly in presence of a drug, if the body converts the drug into a toxic product, which has been shown to cause death in 1 in 300 of these cases [27]. These figures suggest that a large portion of the total global population could be affected by this condition and suggest that more attention should be given to this discrepancy when it comes to finding a suitable treatment.

The genetics of the cytochrome P450 enzyme (CYP) has been a highly studied because it is extremely polymorphic [27]. One enzyme in this family is CYP2D6, which is essential in the metabolic pathway of 100 common drugs, many of which are prescribed to treat CVD. Its most prevalent allele has a frequency of 28.6% and is responsible for about 70% of the cases of individuals with loss of ability to metabolise drugs resulting from the CYP2D6 enzyme [27]. That particular allele causes the enzyme to have no function at all, because some critical genetic material is cut between transcription and translation of the DNA.

This mutation is known to have different effects on different ethnic groups as well. In terms of phenotypic frequency (because this is a recessive trait, it means that the individual has two copies of the allele), the European and North American Caucasian population have prevalence between 5 and 10% while it has a 1.8% frequency in the African American population [27]. However, a much larger percentage of the population is mildly affected by the polymorphism, since 32% of the Caucasian population is heterozygous for the allele, meaning that they have one copy of a normal gene and another defective copy [27]. The phenotype for heterozygosity has a more mild effect than the full-blown version of the allele.

In addition to pharmacokinetic variation, the properties of drugs are also affected by the pharmacodynamics due to polymorphisms in drug targets. An example of this is "aspirin resistance" in stroke and cardiac patients. Aspirin is used to prevent arterial thrombosis or clotting by preventing platelet aggregation, however, it does not prevent platelet aggregation in approximately 10% of stroke and cardiac patients [26]. It is thought, but yet not proven, that this is due to polymorphisms of genes that encode for fibrinogen platelet glycoprotein receptor GPIIIa [26]. Similarly, polymorphisms in genes encoding for diuretic and lipid lowering drug receptors impact on the pharmacologic responses individuals have to these medications.

Genetic variations in individuals susceptible to specific CVDs also influence the pharmacogenomic properties of medications [26]. Examples include how heart failure and hypertension affect how individuals respond to CVD pharmacotherapy. Patients with metabolic syndrome are known to have varied responses to a number of medications used to prevent coronary events, including aspirin, β-blockers, angiotensin regulators as well as antidiabetic therapies and lipid lowering agents due to polymorphisms in genes encoding for receptors and second messengers that may be unique to patients with the disease [26]. In the future, the genetic profile of an individual with a specific disease may help physicians decide which medications should be used to treat the disease.

How an individual may respond to therapy is also dependent on interactions between genetics and biological factors, which can be either "constitutive" or "acquired" [26]. Constitutive factors include age, gender and ethnicity while acquired factors include diet, alcohol use, tobacco use and exposure to pollution. Age and gender related differences in pharmacological properties of medications most often exist due to changes or differences in pharmacokinetics and pharmacodynamics. For example, several polymorphisms in cholesterol ester transferase in males but not females have been correlated with poor response to pravastatin, a cholesterol lowering agent [22].

Finally, genetic and environmental interactions with acquired factors impact the pharmacogenomics. As an example, the negative effects of smoking on CVD risk are greater in individuals with a variant in the APOE genotype and smoking affects the pharmacokinetics and pharmacodynamics of CVD medications in

individuals with different genotypes [26]. Several gene environmental interactions have been shown to impact individual response to therapy [26] and expanded studies in this area are clearly needed.

Use of Pharmacogenetics and Pharmacogenomics in CVD Treatment

Shortcomings in the current treatment of CVD call for a new, more effective approach to identify appropriate medications and doses to treat CVD according to an individual's genotype. Recent and rapidly accumulating evidence is beginning to point toward genetic and genomic factors, alone and taken together with environmental factors, as being of considerable importance in determining interindividual variability in drug responses. Since it is clear that genetics plays a role in how a patient responds to treatment, genetics can also play a role in how a drug or treatment is administered. Pharmacogenetics and pharmacogenomics are expected to optimise therapy and reduce toxicity through genetically guided, individualised therapy that takes into an individual's genetically acquired ability to metabolise and respond to the drug [25]. In the instance of CVD, the dosage of the drug would be tailored to the individual's ability to metabolise and absorb a drug as well as their ability to respond to the medication based on the individual's genetic profile and the environment in which they live.

The ability to predict response may have profound implications. As an example, most heart failure therapies lead to a reduction in blood pressure. In patients who achieve controlled blood pressure easily, this may limit the ability to add other therapies that also have potential for benefit. Should an individual's genetic profile determine that a patient is unlikely to derive benefit from a certain drug (e.g. β -blocker), then this drug class might be withheld, allowing other potentially beneficial therapies to be given. Thus, it is hoped that such insights into the genetic basis for benefit to therapy will be revealed in the upcoming years [23].

Another way that pharmacogenomics might improve patient care is through identification of patients at risk for toxicity with cardiovascular medications. Fortunately, most cardiovascular medications are very safe and serious toxicities are rare; however, there are certain cardiovascular medications that have serious toxicities, for which a priori identification of risk would be helpful. For example, genetic polymorphisms in the enzyme responsible for metabolism of cumadin have been associated with reduced enzyme activity and increased risk of bleeding. Should a genetic test be developed that could predict those at risk for impaired cumadin metabolism, then cumadin dosing might be individualized from the outset of therapy [25]. There are already data linking genetic polymorphisms with response to ACE inhibitors, diuretics, β-blockers and ARBs.

The pharmaceutical industry has begun to use pharmacogenomics in several ways. The first is to facilitate the identification of disease associated drug targets through high-throughput SNP mapping, thereby reducing attrition in early phase clinical trials [28]. The second is to genetically profile responders and non-responders early in Phase II drug development such that subsequent large Phase III trials could focus on responders thereby reducing costs [28]. This strategy was used successfully for the approval of trastuzumab on the basis of tumour response to therapy [28]. The FDA and other regulatory agencies have begun to implement key initiatives that are intended to stimulate the use of pharmacogenomics in drug development, and to foster improvements in drug product safety and efficacy [29]. This regulatory support of the use of pharmacogenomics is not only limited to new therapies and diagnostic tests in development, but to older, marketed drugs such as cumadin in the post-marketing period to improve their risk/benefit ratio by optimizing or individualizing dosing.

The promise of pharmacogenomics lies in its potential to identify sources of interindividual variability in drug response that affect drug efficacy and drug safety [27-29]. Although pharmacogenomic testing has been predicted to be one of the first broad applications of genomics to clinical medicine, such applications have been limited to a few tests that are used mainly within academic referral centres [24]. It seems highly

likely, however, that the next decade will see the clinical availability of genetic "drug responder" tests that will allow physicians to further individualise the drug therapies they prescribe [25].

Possibilities in Gene Therapy

While pharmacogenetics and pharmacogenomics have the potential to improve current drug treatments, it is not a permanent answer to CVD simply by virtue of the fact that drugs are not a cure. Although CVD drugs can alleviate symptoms or reduce a risk factors, such as lowering blood pressure, etc, frequently these powerful CVD drugs often have negative side-effects and patients often do not take medication as needed to control their disease. The quest for permanent solutions that is currently being studied involves gene therapy—a potential one-time treatment for CVD. Gene therapy involves the introduction of a normal or modified gene sequence to correct a dysfunction or treat a disease.

According to the study in Greece, there are at least 6 potential targets for gene modification in the development and progression of atherosclerotic disease [30]. These range from using gene therapy to modify risk factors to promoting the growth of new blood vessels (angiogenesis) following tissue injury that occurs following a heart attack. [30]. Many CVDs are amenable to gene therapy protocols and success has been realised experimentally, particularly in the treatment of ischemia, late vein graft failure, atherosclerosis, thrombosis and hypertension. [31]

One of the problems that gene therapy faces relates to the method whereby genes are transferred to the host cell and the vectors that are used to achieve this. The four main methods used to transfer genes into the vasculature tissues are: *ex vivo* gene transfer to vessel segments, which are subsequently transplanted into the host; and gene delivery using cell-based genetic modification, whereby host cells are transduced *ex vivo* to express therapeutic genes and then transplanted back to the host; local or systemic *in vivo* gene delivery, which uses catheters to infuse vectors at a specific or systemic site, respectively [31]. Adenoviral vector and plasmid DNA technology have improved transmission and expression efficiency in myocardial and skeletal muscle tissue; however, increased transmission efficiency and reduced toxicity as a result of inflammatory and immune responses are needed [32].The advancement of non-viral vector technology will allow for efficient gene transfer while avoiding the safety concerns associated with viral vectors [31, 32].

After extensive investigation in preclinical studies and recent clinical trials, gene therapy has been established as a potential method to induce therapeutic angiogenesis in ischemic myocardial and limb disease. [32] Phase I and II clinical trials have demonstrated the safety and suggested the efficacy of gene transfer in therapeutic angiogenesis for coronary artery disease (CAD) and peripheral vascular disease (PVD) and have found minimally invasive catheter-based and surgical techniques of delivery to be effective [32]. Despite this success in localised gene therapy, however, it will be some time before gene therapy becomes a reality for the treatment of systemic human CVD.

Practical and Ethical Issues of Genetics

Implementation of genomics and molecular diagnostics in health care practice will not occur unless primary care physicians are enabled to promote the uptake and application of genomics technologies and its lessons learned. If pharmacogenomics is to be translated into individualized drug therapy, a concerted effort will have to be directed to the 'genomic' education of all healthcare professionals as well as patients [24]. In the future, primary care providers will be expected to provide genetic testing and consultation services. All reports on the knowledge and attitudes of family physicians on the subject of genetics and molecular diagnostics have emphasised the need for education and training. Barriers to implementing such tests in general practice include the inability of primary care physicians to interpret genetic test results and provide appropriate counselling, lack of understanding the concept of risk probabilities and unfamiliarity with

ethical issues. An example of such a dilemma is the following: what should the physician say to the patient whose genome scan suggests the patient has a 31.2% probability of having a heart attack in 5 years time, that the gene is monogenetic and that lifestyle or environmental changes are unlikely to change the prognosis?

In addition to practical issues, there are also issues of confidentiality and ethical issues as to how data that will be generated through genetic testing is managed. As such, there is a need to develop tools to address ethical issues that arise as we move forward on the path to genetic screening, pharmacogenomics and gene therapy [24]. Transitional ethics tools that will be needed include: educational materials and sessions on ethical issues for GP's; printed information and web-based communications on genomics for policy makers, physicians, patients and ethics boards; and, special modules for each targeted geographic area.

Future of Genetics and CVD

Until the "magic bullet" is available, research, particularly in low to middle income countries should progress in a logical, stepwise fashion that can be implemented practically. As mentioned earlier, recent evidence suggests that although variation in genotype frequencies across diverse populations may affect the number of individuals at increased risk for a disease, the genetic effects of these variations are consistent across traditionally defined 'racial' or ethnic groups [6]. As such, it is logical that scientists conducting research in low-income regions should compare the phenotypic, genetic and immunological profiles of these distinct populations in order to elucidate genetic, immunological and environmental interactions that contribute to CVD according to geographic location. This should be done with an objective to find genomic determinants of pharmacological response that can be correlated with phenotypic markers, which, in turn, can be utilised in day-to-day clinical practice settings. Research should then focus efforts on prevention by predictors through randomised trials to test aggressive pharmacotherapy (with medications available to the general population) in the absence of clinical complications of disease. It is anticipated that the strategy will result in considerable benefit to patients through the discovery of phenotypic markers that are practical to assess and thus suitable for cost-effective application in routine day-to-day practice.

Genetic screening is unlikely to be practical on a broad scale worldwide, at least in the short term. More research needs to be conducted in the area of gender inequity for CVD, examining the reason that the majority of CVD victims are women. It will become increasingly necessary to simultaneously study genes encoding a variety of proteins that participate in both pharmacokinetic and pharmacodynamic 'pathways' to evaluate the full contribution of inheritance to variation in drug response. This will require large, well-controlled studies that have been designed especially to test pharmacogenomic hypotheses [24]. To achieve this, more resources need to be allocated to research and other programs that will pursue further investigation of genetics and the interactions between genes and the environment in CVD.

To begin, national governments can encourage scientific, political and public awareness by acknowledging a role for genetics in public health policy. This means establishing more research facilities, promoting public consciousness of genetic predispositions, and making screening facilities accessible to individuals through government subsidies. Only an informed individual, fully aware of his/her dispositions and risks, can make lifestyle choices suitable for his/her health. The goal of this campaign is prevention.

Acknowledgement: We acknowledge the contribution of Professor Pavel Hamet, Directeur de la Recherche, Centre Hospitalier de l'Universite de Montreal, Montreal, Canada, to this paper.

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