Genetics and heart disease

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ABSTRACT

Production of genome sequence has recently skyrocketed with many advances in the understanding and etiology of certain diseases. Researchers have localized a region of the human genome that plays a role in determining a person's susceptibility to myocardial infarction. A new apolipoprotein gene that influences triglyceride levels in humans is also described. A recent study from Finland showed that certain families are likely to carry a genetic form of insulin resistance syndrome that predisposes them to accelerated atherosclerosis. Researchers identified 3 mutations in the gene producing a protein called metavinculin, which appears to be linked to abnormalities in cellular structures and function in patients with dilated cardiomyopathy. Gene therapy has emerged as a genuine therapeutic option with the potential to alter the manner in which cardiologists manage the 2 most common cardiac disorders - coronary artery disease and congestive heart failure. Along with angiogenesis and gene therapy, cell transplantation is one of the newest treatment modalities proposed to improve the outcome of patients with cardiac failure. Two major advances in stem cell therapy for cardiovascular disease were published recently. They demonstrate how bone marrow stem cells can regenerate myocardium in the infarct area of a mouse heart. A German Cardiologist has for the first time successfully transplanted a patient's own stem cells in an infracted area in the heart. This review summarizes the current knowledge of the genetic associations with cardiac diseases.

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Since the publication of the human genome 2 years ago, there have been many changes in the field of genetic research, and it has provided investigators with a vast new array of potential therapeutic genes to test in animal models and in vivo.[1] As more and more of the human genome was discovered, new associations between genes and diseases were identified, and the possibilities for genetic medicine became apparent. This overview summarizes the most recent advances in genetic research in the field of cardiac disease.

Atherosclerosis. Most common chronic diseases, including hypertension, type II diabetes, and coronary heart disease (CHD), appear to depend on the interaction of environmental risk factors and multiple predisposing genes. Certain aspects of the pathophysiologic characteristics of CHD are understood, but the relative importance and the interplay of various factors relevant to this disease are still poorly defined. Thus the number of genes involved in its pathogenesis, as well as their relative importance, is speculative. The study of genetic abnormalities related to lipid metabolism provides an example in which a genetically determined factor was discovered in premature CHD.[2]

Researchers from Germany and the United States of America (USA), report they have localized a region of the human genome that plays a role in determining a person's susceptibility to myocardial infarction (MI).[3] In the past, chromosomal loci have been linked to specific risk factors like hypertension, diabetes and hypercholesterolemia. Investigators of this latest research claim this is the first time an apparent genetic predisposition to MI has been linked to a certain region on chromosome 14. A person with moderate cholesterol levels, or hypertension, for example, might go on to have a myocardial infarction if he or she also had the "MI susceptibility gene," whereas someone without this genetic variant would be less likely to have an acute cardiac event.

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Broeckel et al[3] describe their analysis of 513 Caucasian families from 7 hospitals across Germany. At least 2 members of each of the families participating had experienced an MI before the age of 59 years or a diagnosis of premature coronary artery disease.

After performing a total genome scan in the 513 families, the authors found that MI risk mapped to a single region on chromosome 14. Specific knowledge of an MI susceptibility gene would also enable genetic testing to guide treatment decisions. Common mutations in the alpha2B-adrenergic receptor (AR) gene and angiotensin gene predict increased risk of cardiovascular disease (CVD), according to 2 studies published recently.[4,5]

In the first study, Snapir et al[4] reports an association between a common mutation (D variant) in the alpha2B-AR gene and risk of acute coronary events. The research is part of a prospective ongoing Kuopio Ischemic Heart Disease Risk Factor Study (KIHD), involving 912 middle-aged men in Finland. The authors found KIHD men who were homozygous for the D variant (21% of the study population) had twice the risk of acute coronary events over follow-up as men with one or no copies of the mutation (relative risk [RR]=2.2, 95% confidence interval [CI] 1.1-1.4, p=0.02, after adjustment for potential confounders). The authors believe that the D variant of alpha2B-AR is a novel risk factor for acute coronary events. The study found no association between the D variant and hypertension.[4]

In the 2nd study, Rodríguez-Pérez et al[5] looked at associations between common mutations in genes of the angiotensin-renin system and CHD. They report that in a case-control cohort from Gran Canaria Island, angiotensin 235T mutation significantly contributed to the development of CHD but not to the development of hypertension (**Table 1**). Furthermore, the absence of this mutation (denoted M235) conferred protection against heart disease. A common deletion mutation in the angiotensin converting enzyme (ACE) gene did not significantly predict CHD, however absence of the mutation (denoted ACE-II) appeared to increase the cardioprotective effect of M235.[5] Pennacchio et al[6] discovered a new apolipoprotein gene that influences triglyceride levels in humans. The authors suggest that their novel gene, christened apoprotein AV(APOAV), could help to identify patients at risk of hypertriglyceridemia, and could offer a new target for treatment. They identified the gene on chromosome 11, just proximal to a cluster of known apolipoprotein genes. The authors report that the gene, like other apolipoproteins, appears to play a significant role in lipid levels, in particular in triglyceride homeostasis. In mice, Pennacchio et al[6] demonstrate that absence of the gene results in a 4-fold increase in plasma triglyceride levels, while over expression of the gene causes plasma triglycerides to drop to one third of the normal level ($p<0.001$).

These findings indicate that [the protein] APOAV is an important determinant of plasma triglyceride levels, a

Table 1 - Risk of coronary heart disease associated with angiotensin and angiotensin converting enzyme polymorphisms in Gran Canaria Islands residents.

Genotypes (% of study population)	OR of CHD*	95% CI	p value
Homozygous 235T (29.1)	1.7	1.1-2.6	0.01
Homozygous M235 (22.4)	0.54	0.36-0.82	0.004
M235 + ACE II (NA)	0.24	0.07-0.77	0.002

OR - odds ratio, CI - confidence interval
CHD - coronary heart disease, * by multiple logistic regression analysis
ACE - angiotensin converting enzyme, NA - not available

Table 2 - Differences in cardiovascular risk factors between early onset coronary heart disease patients and their unaffected siblings.

CV risk factors (mean)	Patients (N=101)	Unaffected siblings (N=54)	p value*
2 hour plasma insulin (pmol/L)	475.7	331.8	0.011
2 hour insulin areas (pmol/L per hour)	796.2	640.4	0.031
Total triglycerides (mmol/L)	1.91	1.68	0.018
VLDL triglycerides (mmol/L)	1.25	1.06	0.011
Fibrinogen (g/l)	3.8	3.4	0.008
HDL-C (mmol/L)	1.22	1.42	0.001

* patients versus unaffected siblings, adjusted for sex
CV - cardiovascular, VLDL - very low density lipoprotein,
HDL-C - high density lipoprotein cholesterol

Table 3 - Bleeding event rates during follow-up in the 2 genotype groups: wild type, and variant (patients who had one or more of the CYP2C9 alleles) type.

Bleeding event rate	Wild type (N=127)	Variant (N=58)
Serious bleeding (per 100 person-years)	4.89	10.92
Life threatening bleeding (per 100 person-years)	0.70	1.56

Table 4 - Improvement in cardiac function following treatment with bone marrow stem cells to regenerate myocardium.

Cardiac function	Treatment group at 9 days*%	p value
Left ventricular end-diastolic pressure	-36	<0.05
Left ventricular developed pressure	+32	<0.05
LV+dP/dt (rate of pressure rise)	+40	<0.05
LV-dP/dt (rate of pressure decay)	+41	<0.05

LV - left ventricular
dP/dt - pressure/time
*% difference when compared to untreated controls

major risk factor for coronary artery disease. Pennacchio et al[6] propose that the mutations in the gene in humans might provide "prognostic indicators for hypertriglyceridemia susceptibility." Furthermore, they suggest, modulation of the APOAV protein could be "a potential strategy to reduce this known cardiovascular disease risk factor." As genetic risk factors for CVD are identified, and they may become part of a screening process to identify individuals at risk, screening patients for genetic risk factors of CVD will be common place in the coming decade, possibly surpassing the efficiency of traditional risk factors. Screening [genes] would possibly become much more efficient than measuring cholesterol, blood pressure, blood sugar, C-reactive protein, or homocysteine. It is quite possible that genetic screening will be the most efficient at accurately defining who are the people who are 90% at risk of developing atherosclerosis before age 40, and so forth.[7] In the long run, studies of angiotensin, angiotensin converting enzyme, ACE, alpha2B-AR and such genes, will be important, but not for identifying disease susceptibility. Instead many believe that these studies will help in the field of pharmacogenetics to understand why some patients respond better than others to a given drug, and to tailor treatments to the specific needs of the patient.[5]

Premature familial coronary heart disease. Families who suffer from early-onset CHD can blame their genes for their premature condition.[8] A recent study from Finland showed that these families are likely to carry a genetic form of insulin resistance syndrome that predisposes them to accelerated atherosclerosis. Kareinen et al[9] studied 101 Finnish patients with early-onset severe CHD who had affected siblings. The researchers compared the levels of various cardiovascular (CV) risk factors between patients, affected siblings, and any unaffected siblings. Kareinen et al[9] found that patients and affected siblings shared CV risk factors associated with insulin resistance syndrome that were absent from unaffected siblings. In particular, the early-onset CHD sufferers shared elevated insulin, triglyceride, and fibrinogen levels, and reduced HDL-C levels **(Table 2)**. This study provides further evidence that genes may play a large role in early-onset coronary heart disease.

A recent large-scale study employing high-throughput genomic technology points to a previously undescribed association between variants in genes for 3 thrombospondin glycoproteins, known to play a role in vascular integrity and thrombosis, and the development of premature familial MI.[10] The investigators used a case-control design and the new high-throughput genomic screening technology to examine common gene variants of a large number of candidate genes in members of 352 families with premature CAD. The families, from 15 participating centers, had to have at least 2 members with CAD. Their CAD also had to be premature, defined as disease prior to age 45 years in men and age 50 years in women. A total of 62 vascular biology genes and 72 single-nucleotide polymorphisms (SNPs) were assessed among 352 confirmed cases of premature CAD drawn from these families, and 418 control subjects. Myocardial infarction was the most common qualifying event in cases, seen in 54%. Three novel SNPs from 3 distinct thrombospondin genes emerged as among the most highly associated variants. Strongest among these was a variant of thrombospondin-4 (A387P), with an adjusted odds ratio for MI of 1.89 (p=0.002 adjusted for covariates) for individuals carrying the P allele.[10] The interpretation of their actual importance relies on considerable further study, requiring independent replication and proof of a cause-and-effect relationship for the variants directly influencing the disease. Our current understanding of the genetic basis of CHD is still primitive. Thus applications to the practice of medicine may be slow to evolve. In principle, genetics research should help identify persons at risk for CHD, but in fact such knowledge is limited at this time. Nevertheless, the study of the gene variants in CHD can be expected to be helpful in understanding the mechanisms of the disease and in developing new therapies.[10]

Cardiomyopathy. Researchers have found evidence that mutations in a gene encoding for protein components of intercalated discs, structures that transmit contractile force between cardiac myocytes, may contribute to the development of idiopathic dilated cardiomyopathy (DCM). Olson et al[11] identified 3 mutations in the gene producing a protein called metavinculin, which appear to be linked to abnormalities in cellular structures and function in patients with DCM. This study suggests that metavinculin plays an important role in the structural integrity and function of the heart, and demonstrates that inherited dysfunction of this protein is associated with altered actin filament organization in vitro, disrupted intercalated disc structure in situ, and DCM. Analyses of the metavinculin-specific exon in genetic samples taken

from 350 unrelated DCM patients were compared to 500 controls. The researchers found 3 previously unknown mutations, one in each of 3 patients. The authors calculated that metavinculin mutations occurred in 3% of familial cases of DCM. The strong influence of genetics in DCM was first made clear 10 years ago with results of a study carried out at Mayo Clinic showing 20-30% of cases were in fact familial.[12] The study stimulated a search for specific genes that might contribute to the development of DCM. Since then, mutations in genes encoding for cytoskeletal, contractile, nuclear membrane, and other proteins have been identified. This study brings to 9 the number of genes currently linked to DCM.

One of the most important messages from this study is to again remind cardiologists that dilated cardiomyopathy is frequently familial, and short of being able to do genetic testing, it highlights the importance of family screening (with an echocardiogram), even if there is not an obvious family history. Olson et al[11] results also provide some theoretical support to why the use of ACE inhibitors and blockers - standard therapy for patients with this condition - may benefit them. They speculate that those drugs, by reducing the mechanical stress on a heart where critical proteins are in a weakened state, might lead to less cumulative damage over time. This understanding will guide further work in this area and in the therapeutic approach to congestive heart failure.

Researchers have spent 40 years trying to unlock the mysterious origins and progression of hypertrophic cardiomyopathy (HCM), now known to be the most common genetic cardiovascular disease (CVD). In a recent review, Maron[13] outlines the most common symptoms and tools for diagnosing HCM, noting that DNA analysis, now 10 years old, is the only definitive test for HCM. Hypertrophic cardiomyopathy is still the number one cause of cardiovascular death in young people, including athletes. The most celebrated development in recent years has been the advent of internal cardioverter desibrillator for the prevention of sudden death. An improved understanding of the genetics of the disease will help to better risk stratify patients and select an appropriate management strategy.

Gene therapy. Over the last few decades, investigators have questioned the mechanisms of many diseases at the physiologic and genetic levels and have made dramatic progress in developing pharmacologic drugs to alleviate these maladies. The next step, already in progress, is to use genes themselves as the drugs replacing or altering the expression of defective genes-to treat patients at the molecular level. Unfortunately, while gene therapy may be to the 21st century what antibiotics were to the last, we have a long way to go before success is at hand. After a decade of preclinical and early phase I clinical investigations, gene therapy has emerged as a genuine therapeutic option with the potential to alter the manner in which cardiologists manage the 2 most common cardiac disorders - CAD and congestive heart failure.[14] Isner[1] expressed hope that preliminary clinical evidence showing gene transfer to be safe and well tolerated should permit larger-scale trials to go ahead, and noted that many of the potential toxicities highlighted by experiments involving angiogenic growth factors of genetically engineered mice have not been borne out in clinical trials. Specifically, clinical trials do not suggest that the use of angiogenic cytokines accelerates atherosclerosis; indeed, the available data suggest that some angiogenic cytokines, such as vascular endothelial growth factor (VEFG), may have a use in preventing restenosis. This strategy is now being tested using gene transfer in patients with lower extremity vascular disease, and trials have already started in patients with coronary artery disease.[15] Isner[1] concluded by noting that the potential to use cell therapy with gene transfer has now been established in preclinical studies and is undergoing initial trials in humans. In the field of cardiovascular disease, over 1000 patients have now been treated in phase 1 trials. There have been no deaths due to the gene or protein therapy alone, although there have been deaths related to the natural history of the disease. Serious side effects have been minimal. On the basis of these findings, phase 2 and 3 trials are now in progress, most with VEGF or fibrobalst growth factor where dosing and clinical efficacy will be evaluated. However, a number of critical questions regarding the technology remain.[15]

Do we have safe and effective means for gene transfer to the heart and do we know where and for how long to express the gene? Most authorities believe that there's still substantial uncertainty here. Gene therapy is also one of the "cutting-edge" ideas being investigated for the treatment of heart failure, which has become a possibility following large advances in the knowledge of the genetic basis for cardiomyopathies. However, some believe that gene therapy may still be many decades away in this field.[15] Finally, gene therapy had multiple "initial" successes followed by the realization that much of the enthusiasm for each success has been perhaps premature or overstated. Further, much of the early excitement with regards to this approach has been dampened following the recent death of a young male involved in one clinical trial. However, as with all discoveries and new fields, problems do exist, and they need to be identified, studied and overcome.

Pharmacogenetics. A recent study published in JAMA[16] showed that hypertensives who carry a common genetic variant may make them more likely to benefit from diuretic therapy. The α-adducin Gly460Trp variant has already been linked to renal sodium retention and salt sensitivity. The authors hypothesized that diuretics, which promote sodium excretion, would prove particularly effective in people carrying the adducin variant. In the future, genetic tests to identify carriers of the α-adducin Gly460Trp variant may help to identify hypertensives who might best respond to diuretic therapy.

A recent study from the University of Washington showed that 2 genetic variants in CYP2C9, the human enzyme responsible for metabolizing the anticoagulant warfarin (Coumadin) significantly increases the risk of bleeding in some patients.[17] Earlier studies had already established a link between patients who have the genetic variations CYP2C9*2 and CYP2C9*3, and low-dose requirements for warfarin, but this is one of the first studies to show an association between these variants and the risk of a serious adverse reaction to the anticoagulant. The findings were based on a retrospective cohort study conducted at 2 anticoagulation clinics run by the University of Washington, USA. The study included 185 patients with a complete history of warfarin exposure, who were treated with the drug for various indications from April 3, 1990 to May 31, 2001. All of the patients were white, Blacks and Asians were excluded. The mean age of the patients at the beginning of therapy was 59.9 years; 63.8% of the patients were male. Just over half (51%) of the patients were receiving warfarin for atrial fibrillation (AF), with a mean follow-up time of 2.24 years. Patients were divided into 2 genotype groups: wild type, and variant (patients who had one or more of the CYP2C9 alleles) type.[17]

As genomic information becomes more readily available, it is likely that clinicians will need to consider new guidelines for patient management, especially when administering drugs with narrow therapeutic indexes such as warfarin. The variant CYP2C9 genotype could be considered a sensitivity factor for low-dose requirements when initiating warfarin therapy, and patients with a variant genotype could be considered candidates for increased surveillance for bleeding risk. **(Table 3)**. With the advances in the genetic era, we believe that we are coming to the stage, gradually, of individualized medicine, of determining who will respond better to certain drugs, or who will be more vulnerable to certain toxins.

Stem cell therapy. Stem cell therapy has recently emerged as a potential hope for those who develop severe heart failure after an extensive myocardial infarction. Two major advances in stem cell therapy for cardiovascular disease were published recently. The first demonstrates how bone marrow stem cells can regenerate myocardium in the infarct area of a mouse heart,[18] while the 2nd describes the use of a subgroup of bone marrow stem cells to stimulate neovascularization and prevent remodeling in the infarct area of a rat heart.[19] In both papers, the stem cell therapy was associated with improved cardiac function.

Wang et al[20] showed that cardiomyogenic differentiation of marrow stem cells (MSCs) can indeed occur in vivo. In this study, isogeneic cultured MSCs were labeled with 4',6-diamidino-2-phenylindole (DAPI) and implanted into the left ventricular wall of recipient rats. After 4 weeks, DAPI-labeled donor MSCs demonstrated myogenic differentiation with the expression of sarcomeric myosin heavy chain, an organized contractile protein in the cytoplasm **(Figures 1 & 2)**. Orlic et al[18] reported that they have identified bone marrow stem cells that, when injected into MI mouse, migrate specifically into the infarct area, replenish it with cardiomyocytes, endothelial cells, and smooth muscle cells, and partially restore cardiac function.

In Orlic et al's[18] study, the stem cells were isolated from donor mice, and injected into recipients in viable myocardium bordering a 3-5-hour-old infarction. Nine days after injection, the researchers observed new myocardium complete with cardiomyocytes and vascular structures filling almost 70% of the infarcted region in 12 of 30 mice. The treated mice showed significant improvement in left ventricle parameters, as compared to untreated controls **(Table 4)**. At 9 days, the new myocardial cells were still proliferating and maturing, suggesting the possibility for further benefit at longer follow-up.

The alternative to bringing new myocardium to the infarcted heart is to help the heart in its own recovery by preventing adverse remodeling. This approach was taken by Kocher et al[19] who identified a subpopulation of bone marrow stem cells with hemangioblast-like properties that, when injected into MI rats, migrate into the infarct zone, generate new blood vessels, and thus keep the hypertrophied cardiomyocytes alive as they work to restore LV function. Left ventricular end-diastolic pressure dropped by 36% and LV-dP/dt increased by 41%. At the 2 week follow-up, the researchers observed significant increases in microvascularity and in the number of capillaries and feeding vessels both within the infarct zone and at its perimeter. The revascularization of the infarct tissue resulted in a 6-fold reduction in myocyte apoptosis, a reduction in scar formation, and a significant restoration of cardiac function. The benefit was sustained up to 15 weeks. Left ventricle ejection fraction increased by 34% (P value <0.001).[19,21] German cardiologist Dr. B. Strauer from Düsseldorf, Germany has for the first time successfully transplanted a patient's own stem cells for MI treatment, on August 24, 2001. Strauer et al[22] transplanted the patient's bone marrow cells into his myocardium after he suffered an MI, and found a significant improvement of the patient's heart function. In their report the researchers detailed that, 10 weeks after stem cell implantation, the patient showed a reduction of the infarct area from 24.6-15.7% of left ventricular circumference and a 20-30% increase of ejection fraction, cardiac index, and stroke volume.[22] Strauer et al[22] assumes that the adult stem cells, which were transplanted into the dead areas of the myocardium, have differentiated into cardiomyocytes, which regenerated the heart wall. Although at this point he could not prove this hypothesis, due to having not yet extracted and analyzed tissue samples from the myocardium, he had no other explanation for the improvement of the patient's heart. After the first successful implantation the team has treated 6 more MI patients with their own bone marrow cells.

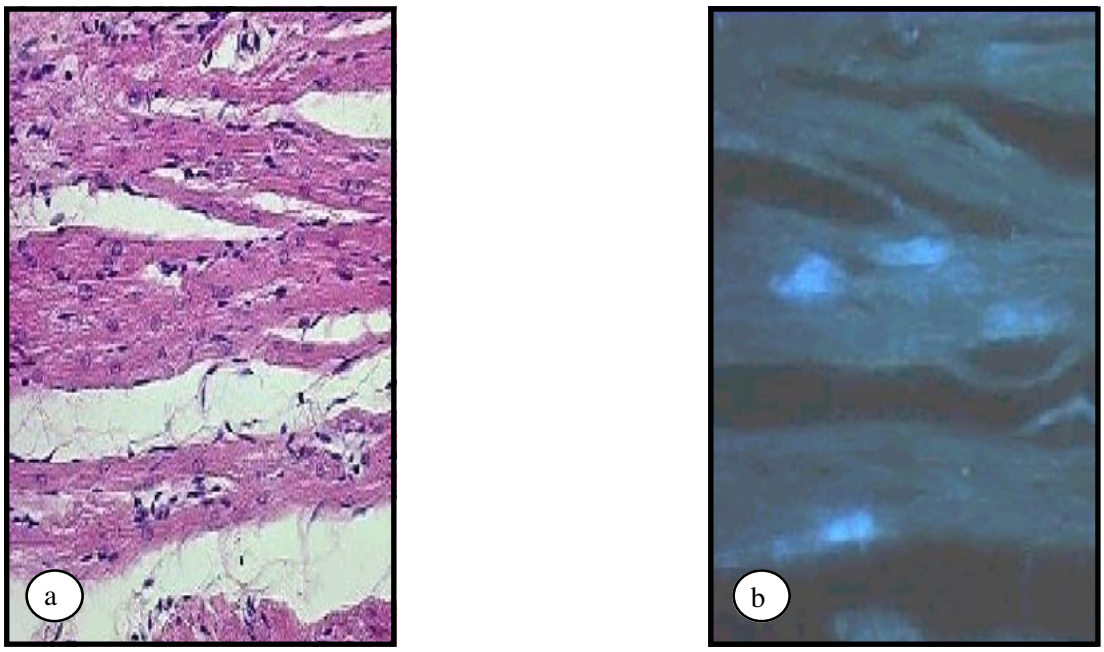

Figure 1 - Marrow stem cell 4 weeks after implantation. **a)** J and E stain, looking like normal myocardium. **b)** DAPI - labelled, implanted cells within the normal looking myocardium. DAPI - diamidino-2-phenylindole

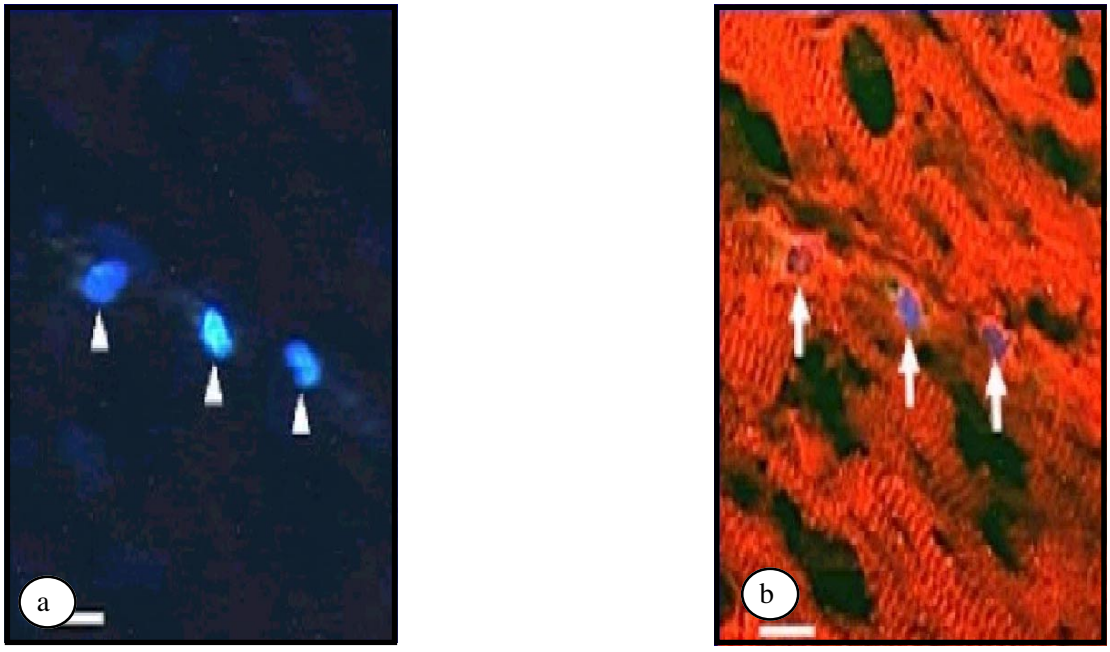

Figure 2 - Marrow stem cell at 6 weeks. **a)** Three DAPI[4,6] labelled cells. **b)** Implanted cells are sarcomeric myosin heavy chain positive (like the surrounding muscle). DAPI - diamidino-2-phenylindole

Taylor[23] advocates myoblasts as the best cells to be starting with in clinical work. Ten years' worth of preclinical data showed that these [myoblasts] appear to be relatively safe in animals, and improve function in animal models of myocardial infarction.

Autologous skeletal myoblast transfer. On June 15, 2000 researchers led by Dr Philippe Ménasché reported the first clinical use of autologous skeletal myoblast transplantation in a 72-year-old patient with heart failure subsequent to multiple previous MIs. He injected 800 million skeletal myoblasts cultured from biopsies taken from the patient's leg, into infarcted tissue on the posterior wall of the heart during double-bypass surgery. Echocardiography and positron-emission tomography scanning prior to the transplant had shown the area to be metabolically inviable. After 5 months of follow-up, these studies reveal contraction in the area of the transplant, the magnitude of which increases when challenged with dobutamine. It doesn't look like normal contraction, but there is an improvement.[24]

French researchers, who have now undertaken autologous skeletal myoblast transplantation in 10 patients with severe ischemic heart failure, report that the technique appears feasible, is generally safe, and has shown some early signs of efficacy. Most patients have had symptomatic improvement and echo studies show new systolic thickening in implanted areas of previous infarct, indicating contractility in implanted segments. These results were presented at the American Heart Association Scientific Sessions 2001 by Dr Philippe Ménasché who claims that we should not let our own enthusiasm hide the reality, and the reality is we do not know anything and we are moving step by step in a very careful fashion. A phase 2 randomized trial of this strategy is currently underway. Only at the end of the randomized trial will we know whether this technique really holds the promise that it is currently expected.

Chimerism. Investigators examining samples of female hearts that were transplanted into male recipients have discovered compelling evidence that cardiac cells not only migrate from the male host to the transplanted heart, they also generate new myocytes as well as endothelial and smooth muscle cell precursors. The finding, reported recently by Quaini et al[25] provides new evidence that the heart can, indeed, regenerate itself. For many generations scientists have been taught that cardiac tissue cannot be regenerated, this concept represents a striking departure from widely accepted paradigms.[26-28] Such a form of chimerism [where cells migrate between the transplanted organ and its recipient] could regenerate myocardium and sustain cardiac performance. The researchers report that 7-10% of myocytes, coronary arterioles, and capillaries in the donor hearts were "highly proliferative" and contained a Y chromosome. They also report that, compared to the control hearts, the transplanted hearts had markedly increased numbers of cells that were positive for the stem cell.[25] Although the presence of Y chromosome cells in the female hearts is fair proof that cells migrate from the host into the transplanted heart, the study still raises many questions. The most intriguing pertains to the origin and developmental potential of the host cells that colonize the graft.[26,27] Further studies are needed to establish this observation.

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Abstract

Genetically determined diseases with neurological manifestations constitute a big public health problem in many communities including Saudi Arabia. As a result of advances in molecular genetics, the bases of several neurological diseases have now been deciphered. A whole series of genes of neurologic interest have been cloned and sequenced. The analysis of human DNA using recombinant technology is fast becoming an integral part of the diagnosis of number of neurological disorders. It is expected that new methods of mapping the human genome will provide us with a valuable approach in elucidating molecular pathology of these conditions and preventing them. This review presents recent advances in molecular neurogenetics and molecular techniques used for gene analysis as a prelude to possible gene therapy.