

Genetic Testing for Cardiovascular Disease Risk: Fact or Fiction?

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Heart attacks, the leading killer of people in the developed world, can be caused by one of a number of conditions, which are collectively labelled cardiovascular disease (CVD). Several companies in the US and Europe now market, or are about to start promoting, genetic tests that claim to identify individuals who are at higher than average risk of CVD. In addition, it is said that some tests will predict a better than average response to certain drug treatments (for example if you are being treated for high blood pressure or high cholesterol). Yet other tests aim to predict whether you are at, for example, high risk of deep vein thrombosis on long airline flights and therefore whether you would benefit from wearing pressure stockings.

How is the validity of these claims to be assessed? How accurate are the tests, and what can the public do if the information given is later found to be incorrect? Finally, to what extent should public access to tests be controlled or monitored? A number of these issues are being considered in the UK by the Human Genetics Commission for a range of DNA-based tests, and here I highlight some of the particular issues and concerns raised by genetic testing for CVD risk.

Genetic Testing for Monogenic CVD

There are some monogenic causes of early CVD where a single gene variant is sufficient to cause the disease. These include Familial Hypercholesterolaemia (FH, see <http://www.heartuk.org.uk>) and Familial Hypertrophic Cardiomyopathy (FHC, see <http://www.cardiomyopathy.org/>). Both of these conditions occur in roughly 1 in 500 members of the general population and, for each, rapid mutation (gene variant) screening methods have been developed by researchers, which are suitable for use in hospital diagnostic laboratories. The screening methods are also appropriate for use in “cascade testing”, where pre-symptomatic relatives of patients are tested for the variant already found in the patient (see the London *IDEAS* website’s, current research section, for further details <http://www.londonideas.org>). To date though, none of the currently marketed kits addresses FH or HCM.

Genetic Testing in Complex Multifactorial CVD

Most cardiovascular disease is not due to a single variant that a patient has inherited. Instead, it is caused by the fact that a person has inherited several different gene variants, each of which has only a small effect on cardiovascular function. By chance, some of us will have only a few of these gene variations while others will have many more.

Simply having some of these gene variations is probably not enough to cause early CVD, unlike the situation in FH or HCM described above. Instead, a combination of several such variants, *plus* being exposed to a “risky” environment, will increase someone’s CVD risk dramatically. Environmental risk factors can include whether or not people smoke, are overweight or have high blood pressure.

This means that for complex multifactorial CVD, predicting someone’s risk purely from a genetic test is not straightforward, to the point where such tests may be of little use.

Genetic Prediction Over and Above Classical Risk Factors

To be useful, a genetic test must provide information that cannot be obtained from measuring classical risk factors (which can be easily, cheaply and accurately measured).

Classical risk factors include personal characteristics such as age, gender, blood pressure, presence of diabetes and degree of obesity. Risk prediction can be improved by including information on environmental factors such as smoking, amount of exercise taken and diet and alcohol intake, all of which are also classical risk factors. When taken together with measures of blood markers such as total cholesterol, or the ratio of the two types of cholesterol (LDL and HDL), these classical risk factors have a very high predictive power.

So, to be useful, a genetic test has to add significantly to this predictive power. The question is whether any of the currently available tests meet this criterion. Research has identified many “candidate” genes, and variants within these genes, which are potentially of value in CVD risk prediction. The commercial tests being proposed

are based on this knowledge. However, because of the multifactorial nature of CVD, the significance of any single gene variant identified by such a test will at best be modest.

The best studied CVD candidate gene is related to lipid (fat) levels in the blood. It codes for a protein called apolipoprotein E (apoE), where the common form is called E3, and where there are two variants, E4 and E2. The changes in the gene that give rise to E4 and E2 alter the function of the apoE protein, so that carriers of the E2 allele (roughly 10% of the UK population) have slightly lower lipid levels. Conversely, carriers of E4 (roughly 25% of the population) have higher levels. Not surprisingly (since we know that high lipids are associated with high CVD risk), E2 carriers have lower, and E4 carriers have higher, CVD risk than the general population. These effects are however very small, and much less important than, for example, the effect of being overweight or of smoking.

In addition, the *direct* result of having one of the variants— high or low lipid levels —is easily measurable. Therefore, measuring lipid levels gives (almost) as much information about an individual's CVD risk as testing whether they have the E2 or E4 gene variant! A similar logic applies to other variants in candidate genes that have been proposed for testing for the risk of, for example, blood clotting or blood pressure.

Companies preparing to market such tests must carry out studies to demonstrate that the genetic information the tests will provide has added predictive value over and above these classical risk measures. Until then, use of these tests cannot be justified, and they are likely to be of little practical value.

Gene Environment Interaction

Since early CVD seems to develop as the result of the *combined* effect of genetic predisposition and a high-risk environment, it is possible that a particular combination may be associated with a particularly high CVD risk. If such a combination could be identified this might be useful in clinical management, for example, in motivating an individual to reduce their environmental risk by stopping smoking or losing weight, or by indicating the need for early and more aggressive therapy (such as drugs for lipid or blood pressure lowering).

One example of this has come from work in our laboratory. UK men who carried the apoE4 allele who were smokers had a particularly high CVD risk compared to E4 “never smokers”. Risk was also low in E4 ex-smokers, supporting the benefit of smoking cessation. Although interesting, such gene-environment interactions need much further work before they could be considered ready for inclusion in any method for risk calculation.

Other problems that remain to be addressed

Size of Risk Effect: Since for all the CVD candidate gene variants identified to date their impact on risk is likely to be relatively small, studies will need to involve very large numbers of people in order to estimate risk with reasonable accuracy. Until these data are available, basing clinical management on “soft” data is unwise at the least, and may be completely inaccurate.

Different Groups: Currently, risk data for the majority of candidate gene variants likely to be included in gene tests are unavailable for women. The same is true for people of African, Indian sub-continent or Asian origin, where a different spectrum of risk factors and predisposition may occur. Thus, using genetic tests based on current data could give potentially completely erroneous results in all but middle-aged, Caucasian men.

Gene-Gene Interaction: At the present time we have essentially no information as to whether the impact of genetic variants on CVD risk are simply additive (as is the case with most of the classical risk factors) or whether more complex interactive effects are the rule. If an individual has inherited a risk variant of one gene and a “protective” variant of another, is the net effect neutral?

Social and Psychological Impact of Genetic Tests: There is still a large degree of concern among the general public about confidentiality and the unknown future impact of genetic information, for example with regard to life-insurance policies, or employment eligibility. Being given genetic risk information may also have an effect on the psychological well being of an individual, with the possibility that family members and friends, or especially employers, could see individuals at high risk as “patients”. In addition, unlike a high cholesterol test result, genetic information may be associated with issues of family guilt about passing “bad” genes on.

Some of these concerns could (and should) be addressed with individuals before and after a genetic test. There is still however the potential concern that gene variants for CVD risk may subsequently be found to be associated with risk for other diseases which may not be so amenable to treatment. For example, the apoE4

variant discussed above is now known to be associated with early onset of Alzheimer's disease. Many people attending lipid clinics in the 1970s and 1980s were given their apoE result, before the Alzheimer's risk was identified and the practice was ended.

Conclusion

At the present time I believe that genetic testing for multifactorial CVD is premature, is at best of extremely limited predictive value, and in many cases may give misleading advice. Although in the future tests based on a battery of thoroughly researched gene variants may become available, it is unclear that they will be of large predictive value over and above measures of classical risk factors.

If however gene variants can be identified that mean people in a particular "environmental" group (such as smokers or those with hypertension or obesity) are at particularly high risk, such tests may be useful.

For any of these potentials to become reality much further basic and extensive epidemiological studies are required.

For more information about the causes and prevention of heart disease see <http://www.bhf.org.uk/>

Acknowledgements

The author is supported by the British Heart Foundation, and a grant from the Departments of Health and Trade and Industry to the London *IDEAS* Genetics Knowledge Park.