Cardiovascular genetics: the ultimate investigation for optimum management?

Stellan Mörner MD PhD and Michael Henein MD PhD

Department of Public Health and Clinical Medicine, Umeå University, and Heart Centre, Umeå, Sweden

Genetic investigations have emerged as an important component of the comprehensive assessment of patients with hereditary cardiovascular (CV) disease. Over the last two decades, genetic investigations have moved on from a proposal into a routine practice, at specialized centres worldwide, particularly in Europe and USA. This resulted in accurate identification of silent family members with clear cut morphological manifestations of disease (e.g. cardiomyopathies) and optimizing their management, e.g. those requiring life-saving ICDs. Likewise, individuals who are gene carriers in the absence of clinical signs of disease will be included in a regular monitoring program. One main advantage of genetic testing is the possibility to reassure genotype negative family members and exclude them from unnecessary long term follow up. Overall, genetic assessment results are of great importance in the family management of monogenic CV diseases. The popularity of genetic investigations has also created a significant market competition with the cost of an individual’s test dropping by a tenfold in the last 10 years, with the advent of next generation DNA sequencing (NGS), which permits massive parallel analysis at a speed that was hard to predict. In addition, cost effectiveness of such investigations is of immense importance. For hypertrophic cardiomyopathy (HCM), it has been calculated that the incremental cost-effectiveness ratio (ICER) is 520 euro per quality-adjusted life-year gained, and 8400 euro per additional life-year gained1. Despite such developments and the relevance in clinical practice of genetic investigations a number of issues related to their clinical applications remain to be addressed.

1. Current international recommendations on the use of CV genetic assessment in routine clinical practice is based on expert consensus. This does not, by any means, undervalue their relevance in the light of the conventional necessary use of randomized controlled trials as the evidence base for recommendations. The latter, in fact, can not be applied in the setting of genetics assessment for ethical and methodological reasons, in addition to the fact that in most cases the genotypic information does not have significant prognostic value in individual patients.

2. Genetics has been recommended as an integrated part of the CV assessment of individuals at risk of developing specific monogenic conditions (e.g. HCM and long QT Syndrome (LQTS)), however in most cases they remain unable to predict those who might develop life threatening complications, e.g. arrhythmia. In addition, reduced penetrance and variable expressivity create problems in assessing the different phenotypes which might prove responsible for the clinical complications.

3. Similar genetic diseases can occur in familial or sporadic forms of disease that will impact the patient and family differently. The same gene for a specific hereditary condition might also be associated with different phenotypic presentations of different clinical relevance e.g. localized single segment hypertrophy versus concentric hypertrophy with dynamic obstructive physiology. Such difference has significant management implications, being conservative in the former and more interventional in the latter. Furthermore, the phenotypic overlap may be greater than that, with the same gene being responsible for completely different diseases, such as dilated and hypertrophic cardiomyopathy being present in the same family.

4. Incomplete penetrance is the rule in hereditary CV diseases, thus making conventional assessment including family history, clinical examination and sometimes genetic investigations insufficient in determining the presence or potential occurrence of a hereditary clinical condition. In addition, there is no recommendation as to the best average age during which genetic investigations for specific diseases should be conducted.

5. Genetics can provide additional diagnosis to a well established clinical and phenotypic condition. An example of this is a gene carrier for HCM who is a patient with long standing systemic hypertension causing concentric left ventricular hypertrophy. The morphological changes in left ventricular structure and function might become difficult to attribute to either of the two diseases.

6. In the setting of common polygenic CV diseases, genetic investigations are very limited in predicting individual’s likelihood for developing acute syndromes, e.g stroke and acute coronary syndromes (ACS). In fact, most patients in everyday cardiology practice have polygenic diseases, with only limited clinical implications. Despite the serious contemporary move towards searching for specific monogenic variants in such conditions, it seems difficult to anticipate that such diagnostic shift, from polygenic to monogenic disease features, would be achievable.

7. Monogenic diseases themselves develop independently of traditional risk factors, which are thus unable to predict patient’s likelihood of developing different disease severities.

8. Methodological issues in genetic investigations are also of great importance, should we start with DNA-analysis of the proband or clinical evaluation of family members, or both simultaneously?. In the case of LQTS, with a high mutation hit rate and relatively low incidence of de novo mutations, starting with a DNA-test can be a rational approach, allowing for pre-symptomatic screening as the first step for relatives. In the case of familial aortic disease (FAD) where only approximately 20% of cases can be genetically verified, it might be more feasible and time saving to undertake a clinical evaluation at the same time as the genetic test, since the chance of finding a mutation is rather low. Some cases will be identified as familial based on the clinical presentation rather than the genotype.

9. Technological advances now allow massive parallel sequencing of DNA, also called Next Generation
Sequencing (NGS). This permits the identification of new, previously unknown, disease genes in hereditary CV conditions, but also creates new problems. Massive sequencing inevitably leads to the discovery of gene variants of uncertain significance (VUS), creating challenges in the following bioinformatic analysis. The limiting step has now shifted from DNA sequencing to bioinformatic interpretation. It is of utmost importance that this is undertaken with precision, given the consequence for the patient and the family, both in the event of a positive or negative genetic test result. Specialized centres, with cardiologists and geneticists in close collaboration, play an important role here.

10. Personalised medicine is of increasing interest, with pharmacogenetic examples like clopidogrel and warfarin, where genetic variants influence the rate of metabolism and efficacy. In the setting of monogenic diseases, the genetic information is most often a confirmation of the clinical diagnosis and permits presymptomatic testing. However, there are examples where the genotype will influence the clinical management, eg LQTS, where the effect of betablockers is related to the underlying genotype.

Conclusion

Genetic investigations for cardiovascular diseases have revolutionized our understanding of some uncommon hereditary conditions. However, despite the accurate gene and polymorphism identification, genetic investigations remain unable to prognosticate for development of acute syndromes as well as serious life threatening complications. Furthermore, the wealth of knowledge created by Next Generation Sequencing is expected to provide its clinical relevance and direct implications remain uncertain, especially in polygenic diseases. In fact, we expect that the massive and sudden increase of genetic information from NGS, with associated interpretation difficulties, will initially lead to a state of “increased confusion” of our understanding of both monogenic and polygenic cardiovascular diseases, but eventually to a more comprehensive knowledge of these conditions.

Correspondence to:
Dr Stellan Morner
Department of Public Health and Clinical Medicine
Umeå University and Heart Centre
Umeå, Sweden
stellan.morner@medicin.umu.se

References