



Taking genes to heart

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Recently, there have been bewildering advances in our ability to read and interpret genetic information. These have come about through improvements in sequencing hardware, coupled with an increase in the density and assignment of single nucleotide polymorphisms (SNPs) and in the bioinformatic techniques needed to process and collate this information. This issue of *Heart and Metabolism* is dedicated to diseases of the heart that follow classical mendelian genetics, and therefore focuses on myopathies and ion channelopathies. In these diseases, candidate genes can be identified on the basis that they encode sarcomeric/contractile, or ion channel, proteins. Such candidate gene approaches to classical familial monogenic disorders are likely to be soon regarded as "old-fashioned" genetics, applicable largely to rare disorders with little global impact on disease burden. This situation contrasts with current trends in genetics that increasingly focus on more common multifactorial diseases in which several genes and environmental aspects interact to cause diseases such as diabetes, hypertension, and ischemic heart disease [1]. Dissecting the genetic components of such multifactorial diseases through association of genome-wide SNPs makes no a-priori assumptions regarding gene candidates, and is therefore likely to uncover novel regulatory pathways.

In a future issue of *Heart and Metabolism*, we hope to cover the more complex genetic contributions that occur in the common multifactorial diseases in which candidate gene approaches have often misled, and have therefore not resulted in reproducible findings. For this reason, this issue of *Heart and Metabolism* makes no mention of genome-wide association studies and the recent findings of SNPs that contribute to common cardiovascular disease [1]. Instead, we focus on old-fashioned genetics which, although implicated in the cause of relatively rare diseases, has a much greater impact on the affected family.

In the Main Clinical Article, Drs Deo and MacRae provide an authoritative overview of the use of genetic screening. The opening paragraph of their article provides an extremely concise précis of the main issues that confound genetic screening: penetrance, genetic and allelic heterogeneity, variable expressivity, and phenocopies. The paragraph is so well-written that it is worth reading a few times, as it provides the foundation for an extremely practical clinically orientated approach to screening that, from the outset, identifies the key limitations to widespread screening, namely genetic and allelic heterogeneity, which often lead to "private" mutations unique to a single family (discussed in the Case Report). Furthermore, because of variable expressivity, even within the affected family, the mutation often does not provide prognostic information. Despite presenting a superb summary of the generic problems in screening for mendelian disorders, Deo and MacRae offer a detailed review of the major phenotypes that may indicate an underlying inherited cardiac muscle disease – namely hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and restrictive cardiomyopathy. For each of these diseases, Deo and MacRae give an elegant and pragmatic summary of the state of the art. Their final conclusions reinforce the use of screening within affected families to provide reassurance and to identify those individuals at risk in whom surveillance and therapy can be focused. These conclusions and other issues raised are further reinforced in the Case Report by Murphy and Gill in this issue of *Heart and Metabolism* and an earlier, high-profile Editorial [2].

The Basic Article by Dr Bezzina focuses on the genetic mutations that cause cardiomyopathy and channelopathies. Our current knowledge of the genes causing these diseases has been concisely tabulated within this review. Bezzina points out that cardiac hypertrophy can also be caused by non sarcomeric

Editorial

Michael S. Marber

protein mutations, copying the classic macroscopic phenotype of hypertrophic cardiomyopathy, but with a markedly different microscopic phenotype: lacking myocyte disarray but instead incorporating myocyte inclusions containing complex polysaccharides or lipid – the so-called lysosomal storage diseases. In addition to summarizing the mechanisms by which mutations in a particular gene give rise to cardiac muscle disease, Bezzina provides an extremely elegant and up-to-date summary of the cardiac channelopathies that cause arrhythmias in anatomically normal hearts. Once again, these channelopathies – namely, long- and short-QT syndromes, Brugada syndrome, conduction disease, sinus node dysfunction, and catecholaminergic polymorphic ventricular tachycardia – can be caused by a variety of mutations in different genes, not all of which in fact encode ion channels. Furthermore, in keeping with Deo and MacRae, Bezzina's emphasis is on the use of screening within families. As she points out, the expressivity of a particular mutation within a family can vary enormously, and in extreme examples no disease is manifest in one carrier who dies in old age of non cardiac disease, whereas in another there can be heart failure or sudden death in childhood. Dissecting the cause for this wide range in expressivity/limited penetrance is likely to be a future area of research activity that will greatly enhance the current position of genetics in estimating prognosis and guiding therapy.

Although the mutations underlying some common genetic diseases such as sickle cell disease and cystic fibrosis have been known for decades, they have not yet led to targeted treatments. In this issue, Dr Sleeper

and her colleagues outline therapies that are already licensed for treatment of the specific lysosomal acid hydrolase deficiencies affecting the heart: Fabry disease and Pompe disease. These are caused by the inability of the lysosome to degrade large complex lipids and sugars, leading to their accumulation in the myocardium, aorta, and valves. The products licensed currently are intravenous cell-permeable formulations of the deficient enzyme. However, Dr Sleeper and her colleagues have pioneered the use of gene therapy using vectors that result in long-term expression of the deficient protein. As beautifully illustrated in this article, these vectors can be tested in a naturally occurring canine model of lysosomal storage disease, in which they result in probably permanent transgene expression (at least 7 years) and, providing they are delivered early in life, they greatly attenuate the disease phenotype. As with other monogenic disorders, gene therapy holds great promise, provided a number of hurdles can be overcome.

This issue of *Heart and Metabolism* provides a comprehensive and contemporary description of monogenetic diseases of the heart. In such a fast-moving field, of one thing we can be certain: an update will be required very soon. ■

REFERENCES

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2. Wolfberg AJ. Genes on the web – direct-to-consumer marketing of genetic testing. *N Engl J Med.* 2006;355:543–545.