One step closer to personalized genomic medicine

Daniel P. Judge*

Johns Hopkins University, Baltimore, MD, USA

This editorial refers to ‘Cardiovascular manifestations in men and women carrying a FBN1 mutation’, by D. Détaing et al., on page 2223

We are rapidly entering an era of personalized genomic medicine. The complete sequencing of the human genome was first announced >9 years ago, and soon afterwards the annotated human genome sequence was available online.1 Today, DNA analysis that was once considered onerous has become routine. Although not perfect, ‘next-generation’ techniques for rapid and low-cost sequencing have been applied to whole human genome determination. The use of massively parallel, high-throughput sequencing to analyse the human genome was first published in 2008 with a reduction in cost estimated from US$100 million to ~US$1 million2. Soon afterwards, two additional whole human genome sequences were reported, with estimated costs reduced even further.3,4 Investigators recently reported whole human genome analysis by another next-generation technique, Sequencing by Oligonucleotide Ligation and Detection (SOLiD) to determine the cause of recessive Charcot–Marie–Tooth disease.5 The estimated cost for this herculean task was <US$50 000, more than the cost of focused analysis of the known genes in which mutations can cause Charcot–Marie–Tooth disease, but the emerging feasibility of this approach is remarkable. As the cost of large-scale genetic testing declines, it will inevitably be used more widely.

Despite profound success in the ability to perform next-generation DNA testing, its application to clinical medicine has been somewhat slower. Today, if a patient showed up in a physician’s office with the full sequence of his or her ~3 billion DNA nucleotide base pairs, its application to medical evaluation and treatment would be nearly impossible. The critical link between genetic analysis and clinical practice will come from large studies that analyse a range of phenotypes that associate with genotypes.

The study by Détaing and colleagues addresses this type of important resource.6 This international consortium of investigators with expertise in Marfan syndrome and related type-1 fibrillinopathies arose from the early efforts to produce a catalogue of FBN1 mutations.7 The Universal Mutation Database now has several locus-specific programmes, including one that focuses on FBN1 (www.umd.be/FBN1/). Both pathogenic mutations and non-pathogenic polymorphisms are designated, and clinical phenotypes are accrued along with the mutations. Similar online resources are available for many monogenic forms of cardiovascular diseases. This type of international collaboration results in far greater numbers than would be available at any single site. Such databases allow one to determine if a rare DNA variant has previously been reported and if it occurs in proximity to known mutations or polymorphisms.

FBN1 mutations typically result in Marfan syndrome, a systemic disorder of connective tissue characterized by its cardinal manifestations: aortic aneurysm, dislocation of the ocular lens, and long bone overgrowth.8,9 The cardiovascular features of this condition were first comprehensively described by one of the pioneers in Genetic Medicine, cardiologist Victor A. McKusick, 55 years ago.10 With only a stethoscope, chest X-rays, and autopsies to evaluate for cardiovascular disease, he reported a full spectrum of aortic and cardiac valve complications related to this condition among 105 people. Since then, affected and at-risk individuals have been evaluated for cardiovascular complications. Although yearly screening is generally recommended, the incidence of late-onset manifestations was previously not known.

Détaing and colleagues now provide data on the cardiovascular risk associated with FBN1 mutations among 965 individuals, excluding neonatal Marfan. While smaller studies have previously addressed the topic, this is by far the largest series for such analysis. Several important points deserve further emphasis. First, the apparent age of onset of ascending aortic dilatation continued throughout the entire span that was represented. Thus, lifelong echocardiographic screening for aortic enlargement should continue despite many years of normal aortic root dimension. The incidence of aortic dissection declined during the period of investigation since 1985, while the prevalence of aortic dilatation remained similar. At first glance, one might expect that this is
due to increased use of prophylactic aortic root surgery. However, there was no significant change in the rates of surgical referral. Possible explanations for this include successful medical treatment, lifestyle modifications, or perhaps simply a decline in the inclusion of people with greater tendency to aortic dissection due to factors other than aortic root size.

Despite suspicion of increased prevalence of aortic aneurysm among affected men with Marfan syndrome compared with women, the evidence supporting this impression has previously been based on relatively small cohorts or anecdotal experience. The study by Détaït et al. addresses this topic in 965 people (53% men). Among this cohort, not only were men more likely than women to have ascending aortic dilatation at age ≤30 years (P = 0.0076), but aortic events (dissection and prophylactic surgery) were also more common among men compared with women, with an adjusted hazard ratio of 1.4. While men tended to have aortic dilatation at an earlier age than women, it is important to recognize that 96% of both men and women in this cohort had ascending aortic dilatation at age 60 years.

Mitral valve prolapse (MVP) is common in the general population and also occurs with type-1 fibrillinopathies. Early echocardiographic studies often greatly overestimated the prevalence of MVP because of incorrect assumptions that the valve was planar rather than saddle-shaped. Improved techniques for imaging, as well as greater recognition of the three-dimensional structure of the mitral valve and its annulus, have led to more accurate determinations of MVP. Population studies have found that women are more likely to have MVP than men. In this context, it is surprising that Détaït and colleagues did not find sex differences in MVP or other manifestations of mitral valve disease among this cohort of individuals. As with aortic disease, MVP was found to be an age-dependent phenotype with increasing prevalence among older subjects in their analysis.

Today there are several reasons to consider the use of clinical genetic testing for people with inherited cardiovascular diseases (Figure 1). For example, recognition of a responsible gene mutation may help to identify syndromic features, to confirm a clinical diagnosis, and to evaluate relatives who are at risk for the condition. However, caution with the use and interpretation of genetic tests is warranted, and genetic counselling should be included with its use. One challenge with regard to personalized genomic medicine is that most families with type-1 fibrillinopathies have a unique or private DNA mutation. This diverse group of disorders includes Marfan syndrome, familial ectopia lentis, familial mitral valve prolapse, MASS (mitral, aortic, skin, and skeletal features of Marfan syndrome), Shprintzen–Goldberg syndrome, some cases of Weill–Marchesani syndrome, and, most recently, the stiff skin syndrome. Attempts to correlate phenotypic manifestations among the fibrillinopathies to specific genotypes have generally failed, with a few notable exceptions. First, more severe manifestations are evident among people with an in-frame or missense FBN1 mutation in exons 24–32. Also, mutations that occur in close proximity to the encoded RGD motif in exon 37 of FBN1 result in congenital stiff skin syndrome, a disorder that appears to provide clues about the role of fibrillin-1 in sclerodermia.

The era of personalized genomic medicine will indeed reach full fruition when a genetic test result helps to determine the best therapy for an individual. Towards that goal, fibrillin-1 mutation or deficiency has been shown to increase transforming growth factor-β (TGF-β) activation and signalling, and therapies that diminish TGF-β effects improve several phenotypic features of fibrillin-1 mutation in murine models. Furthermore, selective blockade of the angiotensin II type-1 receptor similarly modulates TGF-β through overlap in post-receptor signalling. Similar observations in people have led to clinical trials investigating the efficacy of angiotensin II type-1 receptor antagonism in Marfan syndrome.

Future directions for this research include determination of the additional genetic and environmental factors that influence outcomes, penetrance, age dependence, and variable expressivity of FBN1 mutations. Today, the finding of a FBN1 mutation cannot tell us when or even if a patient will develop cardiovascular manifestations such as mitral valve disease or ascending aortic dilatation. With lower costs and expanding use of genetic analysis, an era of personalized genomic medicine is moving closer but is not yet fully realized.

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References


