Opinion

Impact of genomics and personalised medicine on current practice of clinical cardiology

Abstract

Recent technological advances in gene analysis have provided the modern day cardiologist additional tools to diagnose and risk stratify the cardiovascular patient. This provides a potential window to prevent disease and to maintain wellness, with personalised intervention, in contrast to the traditional approach of treatment to ailment. Many genetic variations predisposing to various cardiovascular pathologies have been described. In some cases the pathological pathways involved are evident, whereas in most heterogeneous conditions the mechanisms remain unresolved. Translational research is progressing in such a rapid pace it is highly likely that coming years will provide the clinical cardiologist many pathways of action for early diagnosis and for targeted treatment. We will review what genomic tools are currently available for the cardiologist to use in routine clinical practice.

Keywords: genetics, sequencing, genes, mutations, clinical cardiology, diagnosis and treatment

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Abbreviations: HCM, Hypertrophic Cardiomyopathy; CPVT, catecholaminergic polymorphic ventricular tachycardia; ARVC, arrhythmogenic right ventricular cardiomyopathy; SVT, Supra-Ventricular Tachycardia; AMP, adenosine mono phosphate; PAH, pulmonary arterial hypertension

Introduction

Genomic and systems biology advances are predicated to change the way medicine is practiced in the future. The focus will be for patient or participant driven effort to maintain wellness and to identify disease onset at very early genetic and epigenetic levels. There is potential for re-alignment of the abnormal biology towards normal with medicine and therapy individualised for that particular participant. This is the basis for so-called personalised medicine and P4 medicine.[1–3]

Implementation of diagnostic tools and risk stratification once a diagnosis is made is common practice in medicine and certainly no different in clinical cardiology. The cardiologist intervenes on those with high estimated risk; there by avoiding future potential complications. The classical example is the CHA2DS2VaSc score to estimate thrombo-embolic risk in non valvular atrial fibrillation.[4] Many other risk stratifications such as TIMI score; Syntax score; Euroscore; Framingham risk score are used routinely in cardiology to guide therapy.

There is much anticipation that gene sequencing will provide early diagnostic tools and further risk stratification models that can be applied in clinical practice. Furthermore there is potential and expectation genomics will guide choice of therapy and doses of medication to individuals.[5] Since the isolation of LDL receptor gene.[6] and hypertrophic cardiomyopathy gene;[7] hundreds of other genes have been linked to cardiac disease either directly or indirectly. The genetic information available on cardiac disease is immense. However; currently the majority of this information cannot be utilised at the bed side in a clinically meaningful manner.

We will summarise the types of genetic tests that are available to the cardiologist. We will also summaries the current understanding of the genetic predisposition to common adult clinical cardiology presentations and assess the impact of genomics to date on routine practice including its impact on currently used medications.

Genome sequencing

DNA sequencing has become faster and cheaper since the new generation sequencers were invented in early 2000's.[8] Better and faster equipment were developed by several competing commercial companies.[9,10] These sequencers use the so-called massively parallel sequencing in comparison to the technique that was initially described by Sanger and Coulson.[11] and used in the early days of the Human Genome Project. The new technology allows vast quantities of DNA to be read accurately and rapidly. The whole genome or the whole exome (protein encoding regions of the DNA) can be sequenced with comparable time frames (and possibly comparable costs) to the original Sanger technique; which; though dwarfed by the capacity of the new generation sequencers; still is the most widely used tool for candidate gene sequencing in clinical practice.[12] In other words; the clinical cardiologist has the option of three types of genomic tests at his disposal; namely traditional Sanger technique or targeted gene sequencing; whole exome sequencing and lastly whole genome sequencing.

Target gene analysis is used widely in clinical practice. For example after identification of a long QT variant in the index case other members of the family have the opportunity to analyse their DNA for the presence of that specific gene variation. Target gene analysis can be performed for gene analysis in the index family member as well. However; the cost associated with sequencing many different variations are higher. With daily discovery of new candidate gene variants (and many unknown variants) target gene analysis may be used less commonly in the future.

In cases with multiple genetic variations; for example long QT syndromes and hypertrophic cardiomyopathy; it may be reasonable to choose whole exome analysis. However; in practice both whole exome analysis and whole genome analysis are research tools and only a few laboratories provide clinical services,[12] target gene analysis provides an answer to a specific question. In comparison whole exome

analysis and whole genome analysis provides a myriad of information on genes that may or may not concern the cardiologist or the patient.[13] Most laboratories separate such incidental findings to actionable; potentially actionable and variants of unknown significance groups. In general actionable variants should be reported to the patient. Such variants include BRCA1 and BRCA2 genes; Colon cancer genes; Long QT and hypertrophic cardiomyopathy genes and hypercholesterolaemia genes.[12] To complicate matters further; the mutations themselves have multiple variations. In arrhythmogenic cardiomyopathy some variations previously thought to be associated and causative are present in the normal population.[14] There is effort to get over this lack of clarity by specifying a signal to noise ratio.[15] Deciphering a genetic analysis and interpreting complex information requires expertise.[16] Even for significant mutations mentioned above there is much debate about imparting such incidental; but critically important information to the patient.[12,15] The information may not only impact on personal life and family members but also impact on employment and health insurance. Given the complexities involved the cardiologist may choose to refer such cases to genetic counselling or to colleagues with broader experience in genetic disorders.

For the purpose of this review; we will classify common cardiology disorders into 'single/oligo gene' disorders and heterogeneous disease. Most 'single' gene disorders are now recognised to be anything but. However; this group of diseases still has a direct but modifiable (via epigenetics) link between the genotype and the phenotype. This is unlike the heterogeneous group where such a link is difficult to establish with the existing clinical and natural history knowledge base for the disease. We will also review the current status of pharmacogenomics relevant to cardiology.

Single/oligo gene disorders

Hypertrophic cardiomyopathy (HCM)

HCM is the most common genetic disorder in the community with a prevalence of 1,500. It is primarily described as a disease of the sarcomere of the cardiac myocyte. It is inherited in autosomal dominant pattern with variable penetrance and expressivity. Diagnosis is usually based on 2D echocardiography. Treatment is based on symptoms and the overall risk assessment for sudden cardiac death.[17] The first gene underlying HCM was discovered nearly 25years ago.[7] Since then 11 other candidate genes have been discovered. Many more causative variants are being discovered using exome sequencing. However; there is no compelling evidence to suggest that any of these genetic mutations relate significantly to symptoms or to risk of sudden cardiac death.[18]

Family screening and counselling with or without genetic testing is recommended by guidelines as part of the work up and management for HCM. Genetic tests may be used to aid the clinical diagnosis; for example to distinguish between other causes of hypertrophy.[19] In clinical practice genetic information does not contribute to the management of the index case. Following genetic counselling genetic tests can be performed on the index case. If a mutation is identified family members can be tested for the presence of this particular mutation. Family members with a mutation are offered imaging surveillance and sudden death risk assessments. It is important to note presence of the genotype does not necessarily mean the subject will develop the phenotype. For example genotype positive; phenotype negative subjects are not advised to avoid competitive sports.[20] Thus many cases are managed with family screening but without the addition of genetic tests to the mix.

The genetic tests commonly performed for HCM are for known mutations with targeted gene testing. Negative result does not exclude the presence of a genetic variation that was not tested. In such cases family members are offered regular surveillance imaging. Exome sequencing for HCM is performed for research purposes. As can be expected many new causative variants and variants with unknown significance are found as a result.[12] With increasing knowledge about the clinical outcomes; it is expected that these variants may get reclassified to a meaningful group. Similarly; whole genome sequencing remains a research tool with regards to the management of hypertrophic cardiomyopathy.

Long QT syndromes

Long QT syndrome prevalence in the community is estimated to be 1,2000 with the majority inherited in an autosomal dominant pattern. In 75% of the cases the defect is in the K+ channels (LQT1 and LQT2) or Na+ channels (LQT3). This account for 75% of the cases of familial long QT syndromes.[19] Diagnosis is based on the 12 lead ECG after exclusion and correction of reversible factors. Treatment is based on clinical risk and presenting symptoms. Risk assessment includes family history, QT interval; age of onset and responses to stress (exercise or pharmacological). The first Long QT gene was identified in 1996.[21,22] Since then 13 genes in total have been identified as causative for Long QT syndromes.[19] Arrhythmia induction could be with stress; exercise or event triggered (LQT1 and LQT2) or at rest (LQT3). Family screening and genetic testing is recommended for long QT syndromes.[19] Exome sequencing is discovering disease causing variants and variants of unknown significance. Certain specific mutations (e.g. trans membrane defects) are associated with higher risk of arrhythmia.[23] However, the type of mutation per se is not considered risk factor for implantable cardioverter defibrillator therapy.[24,25] A negative genetic test does not exclude familial Long QT syndrome. Positive test will enable family members to be tested for that particular mutation. Regardless of the genetic test result first degree relatives should be screened for Long QT syndrome and risks assessed. Either specific mutation tests or exome sequencing may be used for Long QT syndrome. The clinician requesting the test should be prepared to account for the multiple possible pathogenic variants in addition to the variants of unknown significance. Whole genome sequencing for Long QT work up should only be as part of a research trial.

Catecholaminergic polymorphic ventricular tachycardia (CPVT)

The true prevalence of this rare condition is unknown but thought to be about 1,10;000.[26] Sudden death may be the initial presentation.[16,19]The genetic defects are within two genes responsible for cardiac calcium handling; one autosomal dominant (ryanodine), the other recessive (calsequetrin).[16] Diagnosis is based on exercise and stress testing. Stress or exercise typically produces ventricular ectopy that may be polymorphic or bi-directional. The first case of CPVT was reported in 1975.[27] So far only two genes have been identified as causative. The ryanodine mutations account for 65% of the cases and more than 100 different mutations have been identified. Prevalence of calsequetrin mutation is about 3-5%. Family screening and genetic tests are recommended for index cases and for all first degree family members. Second and third degree family members should undergo clinical evaluation including stress testing. Since the initial presentation could be sudden death; and a clinically valuable risk estimate tool does not exist; mutation positive family members

are offered treatment.[19] Genetic counselling followed by genetic tests for the known mutations of the Ryanodine receptor is reasonable. It is important to request for the entire ryanodine exome to be mapped since some laboratories target only the major clusters.[19] For those with a negative result for ryanodine mutations, calsequetrin tests should be offered. Again; the clinician requesting the test should be prepared for unknown variants.

Brugada syndrome

Brugada syndrome; a cardiac channelopathy with autosomal dominat inheritance; and is thought to be responsible for 12% of cases of sudden cardiac death.[28,29] Diagnosis is usually based on an abnormal ECG with characteristic ST elevation in the right pre-cordial leads. Prevalence varies from 5-10 per 10; 00 in the community and higher in south-east Asian communities.[29] Since identification of the first genetic defect (cardiac sodium channel) close to 350 other genetic mutations have been described in 15 different genes.[29,30] However; only 25% of cases with Brugada Syndrome have a positive genetic test.[31] Since the clinical management is not altered by the presence of a gene defect such tests are not recommended for Brugada syndrome unless for purposes of research.[19] Family members should be screened but genetic testing is not recommended.

Arrhythmogenic right ventricular cardiomyopathy (ARVC)

ARVC is a disease of desmosomes with mostly autosomal dominant inheritance that can lead to cardiac arrhythmia; heart failure and death. Population prevalence is thought to be 1,5000.[32] Diagnosis is on satisfying criteria based on ECG characteristics; the ventricular tachycardia morphology and imaging.[33]Though initially thought to be secondary to mutations in genes coding for a handful of desmosome genes the disease process is now understood to be much more complex and may be requiring multiple 'hits' for phenotypic penetrance.[34] diagnostic criteria do not incorporate genetic results and clinical management is also independent of the presence of mutations. Though targeted gene testing can be useful; in general genetic tests are not recommended for patients with ARVC.[19] Family members should be offered genetic counselling and offered clinical screening and follow up.

Progressive cardiac conduction disease

This artificial group of diseases includes sinus node disease.[35] familial heart block.[36] and characterised by delay in conduction of electrical impulses along the cardiac conduction system. This is to be distinguished from the more common conduction abnormalities that is encountered in clinical practice that are due to structural heart disease. The diagnosis of inherited conduction disease is one of exclusion of all other causes for such abnormalities. The mode of inheritance is thought be autosomal dominant in most cases. The management is based on symptoms alone and usually involves implantation of a pacemaker. The genes associated with cardiac conduction disease are cardiac sodium channel.[37] (majority of the cases) and cardiac calcium channels. Genetic tests for this group of patients are usually for research only. Genetic results do not contribute to risk and intervention is for symptoms only. Thus genetic tests are not recommended.[19]

Dilated familial cardiomyopathy

Cardiomyopathy usually presents with the syndrome of heart failure. Within the subgroup where the underlying pathology is uncertain; a familial cause is found in up to 35%.[38] The most common responsible genes are the intermediate filament protein coding Lamin A/C gene and cardiac sodium channel genes. However by 2011, 31 different genes causing dilated cardiomyopathy were described.[39] with defects in structural proteins; ion channels, nuclear envelope, mitochondrial disease and cytoskeleton proteins.[40] Most of the inheritance is autosomal dominant, with mitochondrial inheritance, recessive and X-linked inheritance also encountered. Family screening of first degree relatives, and if possible up to 3 generations is recommended.[19] The presence of Lamin A/C and Desmin myopathy genetic mutations indicate higher risk of sudden death and implantation of defibrillator may be considered based on the genetic result.[41] A negative test does not exclude familial cardiomyopathy and family screening with imaging and follow up is recommended. The genetic test could be targeted for the high risk mutations. As mentioned in the sections above; Exome sequencing and genome sequencing will uncover more variants some probably causative; some of unknown significance. The clinician should be prepared to account for the results.[42]

Hypercholesterolaemia

Hypercholesterolaemia is an important modifiable risk factor that drives coronary artery disease. The diagnosis is made on a fasting lipid profile test. Severe hypercholesterolaemia is defined as LDL of 190mg/dL (>4.9mmol/L).[43] The risk of coronary disease is related to the cumulative lipid load in plasma over the years [44,45] Many therapeutic interventions are available and more are therapies are around the corner with PCSK-9 inhibitors. The primary gene involved is the LDL receptor gene. 9 different types of mutations were initially described in 1986 .[6]. Since then two other major genes Apo-protein B (ligand for the LDL receptor) and PCSK-9 (enzyme degrading LDL receptor) responsible for LDL metabolism have been identified. So far>1600 different mutations have been described for LDL receptor alone.[46] These account for up to 85% of cases of familial hypercholesterolaemia. The inheritance is autosomal dominant. However in many patients with LDL levels>4.9mmmol/L, no mutation is identified in the three major genes mentioned above (using next generation sequencing for specific mutations or whole exome sequencing). Thus it seems most cases of familial hypercholesterolaemia are polygenic.[47] The typical cardiology patient with LDL elevations to<4.9 are highly likely to have polygenic or environmental contribution to their dyslipidaemia. The cholesterol level and the cumulative load in particular contribute to the coronary artery disease risk; not the presence of mutation.[44] Accordingly genetic tests are not recommended for familial hypercholesterolaemia. Instead the index case is treated aggressively with lipid lowering therapy.[43] Family screening is recommended and those with the phenotype treated. As mentioned above specific mutation tests or whole exome sequencing could be performed to identify genetic basis for hypercholesterolaemia.

Heterogeneous disease

Coronary artery disease: The usual presentation of coronary artery disease is ischaemic chest pain and or a myocardial infarction. The traditional risk factors are well defined and include family history. The modifiable risk factors include smoking; hypercholesterolaemia; diabetes; hypertension and obesity. Significant family history is not modifiable. Therapy and intervention is based on symptoms and not reliant on genetic predisposition. Modifiable risk factors are a therapeutic target to prevent disease progression. This approach is likely to continue for the next decade. What initiates plaque rupture is unknown. Thus there are no clear attributable genetic links to

myocardial infarctions persec.[48] Genetic associations for coronary disease were initially reported in 2007. Since then close to 50 such genetic variations have been described.[49,50] Such associations are discovered by whole genome sequencing (in contrast to whole exome sequencing or target gene sequencing). Without new generation gene sequencing technology such discoveries are unlikely to occur. It is noteworthy most of the reported associations are located away from protein encoding regions. Thus it is likely that these genetic variations influence regulation of gene expression or down-stream pathways. Association studies require large numbers of patients to identify significance. This is due to the fact that 50% genetic associations implicated with coronary artery disease are present in more than half the population and 25% is present in 75% of the population. The relative risk is in general minimal. It is also noteworthy that the majority of the associated genetic variations are not influencing the traditional risk pathways of hypercholesterolaemia; diabetes or hypertension. Thus the pathways through which these genetic variations contribute to coronary artery disease remain unclear. There is active research into this field and immunological mechanisms seem to be the for runners.[48] Genetic tests are currently not recommended for coronary artery disease; unless for research purposes. Genetic tests do not modify the current management of coronary disease; which is based on symptoms. Whole genome sequencing is required for association tests.

Atrial fibrillation and other supra ventricular tachycardias

Atrial fibrillation is diagnosed by 12 lead ECG or a rhythm strip. The management is focused on identifying a precipitating cause; reducing thrombo-embolic risk and rate or rhythm control. In a minority of patients the disease has no discernible traditional risk factor and may be labelled as lone atrial fibrillation and there may be familial pre-ponderance. Management of lone atrial fibrillation is no different with regards to reducing thrombo-embolic risk and rate or rhythm control. Based on traditional Sanger techniques the first genetic link was discovered in 1997.[51] in families with atrial fibrillation and the gene isolated in 2003.[52] The gene was coding for a cardiac K+ channel. Other genes identified in family studies code for natri uretic peptide pre-cursor and an atrial structural protein (discovered with whole genome sequencing) considered pivotal in embryonic development of the heart.[53] There are now many known genetic associations with AF. Atrial fibrillation may reflect a condition requiring two or more 'hits' to express the phenotype. The underlying genetic risk will vary depending on whether there is a direct candidate gene or whether there is an associated variation. There is the possibility that atrial fibrillation secondary to K+ channel mutations may behave differently to medications and therapy.[54] However; this is yet to be proven. Currently; genetic tests are not recommended for atrial fibrillation. The therapy and interventions do not depend on genetic results. Genetic mutations have been identified for supra-ventricular tachycardia (SVT) dependent on accessory pathways (Wolf-Parkinson-White syndrome). The gene codes for a cardiac AMP (Adenosine Mono Phosphate) activated protein kinase.[55] No genome wide association studies are available for SVT at the time of this manuscript. Genetic tests are not recommended for SVT.

Essential hypertension

Hypertension is highly prevalent in the western society and contributes significantly to the cardiovascular mortality and morbidity. Diagnosis is with properly conducted blood pressure measurements and if required ambulatory measurements. For uncomplicated hypertension the target is 140/90, and stricter with other co-morbidities.[56] Essential hypertension is considered to be multi factorial and up to 60% may be secondary to genetic preponderance.[57] There is no one direct genetic mutation responsible for essential hypertension.[58] A recent review into genetic and epigenetics of essential hypertension identified 130 genes with multiple associated variations (whole genome sequencing; whole exome sequencing).[59] There seem to be a correlation between the number of variants associated with hypertension and the level of the blood pressure. None of these associations are predictive of higher risk and do not provide additional information for specific therapeutic interventions. Accordingly, no genetic tests are recommended for essential hypertension.

Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a relatively rare condition with a prevalence of 15per million. Pulmonary hypertension has a poor prognosis with 15% mortality within the first year with treatment.[60] A subgroups of PAH; familial or hereditary pulmonary arterial hypertension is linked to mutations of the bone morphogenic protein receptor 2. This is inherited in an autosomal dominant pattern with variable penetrance and genetic anticipation. In addition to this gene other genes and mutations have been described recently.[61] This area is subject to intense research and the likelihood of further breakthrough is high.[62] For idiopathic PAH that may have familial preponderance genetic testing is recommended following genetic counselling (specific mutations or whole exome sequencing)[61]. Family members may then be checked for any specific mutations identified in the index case. The results do not indicate higher risk and treatment is based on the phenotype.

Pharmacogenomics

Many pharmaceuticals with trial proven benefit are available for many cardiovascular disorders. There is marked variability with regards to efficacy and also toxicity. This limits the net benefit for the individual. Pharmacogenomics is the field where the best medicine in the best dose is identified for each individual based on the genetic variations in drug metabolism.[5] This area is progressing rapidly in some specialities, in particular oncology and haematology where a specific mutation determines the therapy. In cardiology we are yet to see any such breakthrough. The closest we have come to genetics deciding the dosing is with war farin. Though genotype guidance provided longer time within therapeutic ranges; genotype guided dosing did not perform better when compared to a clinical guided dosing for warfarin.[63,64] There is significant controversy with regards to clopidogrel doing and genotype.[65] Clinical guidelines do not recommend genotyping for clopidogrel. There is evidence to suggest that perindopril therapy could be adjusted depending on genotypes for Bradykinin receptors and Angiotensin II receptors.[5] These are yet to be proven in clinical trials. Beta blocker therapy and beta receptor polymorphism has also encountered controversial results. Similar conflicting results have emerged from studies looking into statin therapy and cholesterol levels with polymorphism in cholesterol ester transporter protein, apo-lipoprotein E, and HMGCoA reductase genes.[5] Thus; currently no genetic tests are recommended for choosing or dosing any cardiovascular medication.

Conclusion

Modern technology has advanced the understanding of the genetic basis for many cardiovascular disorders. Though many mutations

and associated variations have been uncovered over the recent years; except for rare instances in cardiology (example CPVT mutation) genetic finding does not relate to clinically significant risk nor guide therapy. In particular the promising area of pahrmacogenomics and personalised medicine has been rather unfruitful for cardiology so far. At the moment genetic tests may be more relevant in providing the index case and the family an etiology for disease; and provide information enabling planning for the future for those affected. There is no doubt however that with the pace with which genomic research is progressing advances will be made in patient care and maintenance of wellness.

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Conflicts of interest

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