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REVIEW ARTICLE

Contextualizing Genetics for Regional Heart Failure Care

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Abstract: Congestive heart failure (CHF) is a chronic and often devastating cardiovascular disorder with no cure. There has been much advancement in the last two decades that has seen improvements in morbidity and mortality. Clinicians have also noted variations in the responses to therapies. More detailed observations also point to clusters of diseases, phenotypic groupings, unusual severity and the rates at which CHF occurs. Medical genetics is playing an increasingly important role in answering some of these observations. This developing field in many respects provides more information than is currently clinically applicable. This includes making sense of the established single gene mutations or uncommon private mutations. In this thematic series which discusses the many factors that could be relevant for CHF care, once established treatments are available in the communities; this section addresses a contextual role for medical genetics.

Pupalan Iyngkaran

Keywords: Congestive heart failure, genetics, indigenous australian, polymorphism, review, therapeutics.

INTRODUCTION

"I have three personal ideals. One, to do the day's work well and not to bother about tomorrow. . . . The second has been to act the Golden Rule, as far as in my lay, towards my professional brethren and towards the patients committed to my care . . ."

William Osler 1849 – 1919 [1]

In many cases medical genetics may be tomorrow's solution, but it is today's question, and done correctly it is in our patient's best interest. In two centuries, humanity has understood its hereditary biology and the factors that can change it. When Mendelian inheritance met Darwinist progressivity, we accepted chance genomic modification and gradual phenotypic evolution as our destiny. We also came to accept that we have no say in the process. A forgotten concept, introduced by the French biologist Jean-Baptiste Lamarck, where inheritance of acquired traits caused by changes in an environment can cause changes in behavior or characteristics leading to an increase or decrease of that phenotype both presently and in future generations, is taking off. His classic example was the stretching of the giraffe's neck to reach treetops [2, 3]. While that extreme is probably unlikely, we have come to accept that he may not have been that far off the mark and that human-environment activity could also affect current and future biology.

In clinical cardiology many examples of genetics have shown increasing importance for pathophysiological explanations. The most common inherited mutations have gone on to explain inheritance patterns for many dilated cardiomyopathies. The more novel and the increasingly studied area of epigenetics have also found clinical correlations. It was noted that during the German introduce food embargo in western Holland, from the resulting famine, the consequent maternal nutritional deficiencies had intergenerational ramifications for mother, child and grandchildren. In Australia, CHF syndromes with comorbidities are epidemic among the Indigenous communities and at younger ages. Evidence continues to show little progress in declining CHF outcomes. It is thus important we give this area important consideration. Population studies have also identified patterns of CHF with different presentations, response to therapies, or pathophysiology with familial associations. These factors have been better illustrated in some communities such as Framingham and increasingly so from those with gene discovery programs [4-11]. The eventual goal for genetics studies would be to enhance "bench to bedside" (and beyond) translation that would allow early diagnosis and institution of preventative intervention to rein in the social and economic costs of

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CHF [12]. In this review we explore genetic factors that could contribute to regional Australian CHF best practice*.

CONTEXTUALIZING GENETICS FOR REGIONAL HEART FAILURE CARE

'After 10 years of concerted effort, ….. clinical genetic testing ….. in cardiovascular disease is a work in progress. One reason is the complexity of the problem. The human genome is far more variable than originally suspected ….. is even more variable than it is now considered to be. With 3 billion bases in the genome, and over 5 billion people on the planet (that is 10 billion genomic copies), the mathematical probability is that every nucleotide in the genome is polymorphic in at least one living individual'.

Gerald W Dorn II [13]

CHF care absorbs 1-2% of health budgets in developed nations. The vast majority of this relates to readmissions. In Australia there are several clear epidemiological patterns. There is an urban and rural divide, and an Indigenous and non-Indigenous divide. Many systems have explored service related themes to close this geographical divide. Some national and state data particularly from Western Australia have shown closing of geographical divides for many Australians but not Indigenous patients [14-17]. It is data like these that poses further questions on the pathophysiology for and contributors to the variations we see in treatment responses between groups.

The CHF syndrome essentially describes the phenomena where the heart or its support systems are unable to supply the body with adequate blood flow to meet metabolic requirements. The most common etiologies are loss of heart muscle from coronary artery disease, long term hypertension and increasingly diabetes, obesity and obstructive sleep apnea. Idiopathic cardiomyopathies are an important established cause in Europeans. In the Indigenous population, studies have noted an access burden at very young ages [17]. There is a high burden of rheumatic heart diseases [18], renal failure, diabetes and most other important comorbid conditions contributing to CHF, in addition to modifiable risk factors such as smoking and alcohol [19, 20]. It will thus be difficult to tease out what is an inherited condition or a predisposition. From the Framingham database one in five cases of HF was potentially heritable [8]. It is thus worth exploring these factors and contextualizing it for a more heterogeneous population.

Cardiovascular genetics has systematically explored most levels within the pathophysiological pathways. The most established science are Genome identification, in the nucleus and now more recently the mitochondria (both organelles containing DNA). This information has relevance predominately for inherited Mendelian genetics or sporadic mutations, and usually identified as single nucleotide polymorphisms (SNPs).Cardiomyopathies, chanellopathies, vasculopathies and indirect contributors such as familial hyperlipidemias and metabolic syndromes are factors that can promote CHF [6]. Advancements have also identified supporting apparatus and their responses under extreme physiological stress. End organ effects of consequence, such as ventricular hypertrophy [21, 22], and pharmacogenomics, in particular adrenergic [13] and RAAS systems [23, 24] and other pharmacogenomic interactions [25-28].

The way genetics has been viewed in CHF has also evolved. Dorn has described the transition from early single gene theories such as the candidate gene theory, to newer hypotheses like the common disease-common variant arguments (cumulative small effects of numerous alleles). Importantly the multifactorial etiology of CHF has provided confounders from which it is difficult to separate the true extent of the underlying inheritance. Thus in the most common CHF model, patients present with multiple contributors, some such a comorbidity which is also subject to their own genetic variations, potential environmental exposure, and from here about one in three have a genetic attributor [6, 29]. New technologies are allowing for deeper and broader exploration of the genome where explanation could vary again. Presently however, terms that have important clinical utility for describing the role of genetics include common (familial) gene polymorphisms, candidate genes, common (sporadic) CHF, risk-modifier or risk-attributable gene effects are clinically relevant for contextualizing CHF at the community level. We discuss three areas of importance.

GENETICS RISK ATTRIBUTORS FOR HEART FAILURE

CHF syndromes have a clear familial predisposition where in 20-30% this risk has one or more genetic contributors. Within this there are perhaps 2 quite distinct clusters, common CHF is more frequent and complex where genetics are not the principal factor. In this form the inheritance is often non-Mendelian as shown in the Framingham Heart Study where CHF risk increases from 1.69 to 1.72 if one or both parents are diagnosed [7]. True familial cardiomyopathies on the other hand develop usually as the result of one mutation, or in a small subset (5%) 2 or more [6]. Identification of these monofactorial determinants started predominately with hypertrophic cardiomyopathies (HCM). In many of these cases there are unique phenotypes that can perhaps be diagnosed from the history and review of echocardiography that would attract a clinician's attention [30]. There also an age-dependent expression which offers screening opportunities, in this case the early teens [31]. Autosomal dominance, variable penetrance and marked phenotypic heterogeneity are characteristics in familial variant. Genetic data has accumulated significantly. Sarcomeric mutations in myosin heavy chain 7 (MYH7) and myosin binding protein C3 (MYPBC3) account for more than 70% of cases, other components are cardiac troponin and light chains around 5%. In 30-40% non-sarcomeric mutations occur [32]. The evolutions of genetics in HCM are important to highlight as the accumulated knowledge has transformed to real clinical applications. The two most noticeable are screening and risk stratification. Offspring from affected parents have a 50% chance of acquiring the gene. Research labs now offer fee-for-service molecular diagnosis in greater than one in three, if there is a family history [30]. This cascade screening approach is only possible because of the accumulated knowl-

*Genetic similarities are more common in groups of people with shared histories, as in a community or race. Thus in the context of genetics and race we use the associations with communities or groups of people interchangeably. There is however no evidence that particular races have different predispositions purely because of race.

edge. HCM is also the leading cause of SCD in young. When all these factors are taken into consideration, the incremental cost per life year saved equates to 14,397 euro for the cascade genetic versus the cascade clinical approaches [33, 34]. Stratifying for sudden cardiac deaths has identified troponin T mutations with sudden death independent of other risk factors. As this only makes up a small percentage of cases, genetics is presently not advocated for risk stratification. What is however important is that new information is adding to efforts to improve risk stratification and develop novel therapies [29-35].

Dilated cardiomyopathies (DCM) manifest with typical syndromic features of poor systolic function and a dilated left ventricle. 1 in 3-4 cases of idiopathic DCM have a positive family history, suggesting a genetic basis. Labelling as idiopathic, where there is no clear etiology, has probably underestimated true familial cases particularly when disease is subclinical in those family members. In 50% of familial cases relatives of probands will be affected and disease can be picked up early [36]. Since 1998 there have been over 40 genes identified, the majority inherited in autosomal dominant pattern that alter many aspects of the myocyte cytoskeleton and contractile apparatus. Only around 30% of cases will there be clear benefits for genetic testing. Unlike HCM most mutations here are low prevalence thus also making it difficult to clinically correlate the pathogenicity. Again the cumulative knowledge is increasingly showing clinical correlation for patient's benefits. Arguments for cascade screening benefits to rule our disease and commence prophylactic treatments are reported [37, 38]. New scoring systems for prophylactic implantable cardiac defibrillators when concern of conduction disease as with LMNA, desmosomal and SCN5A mutations could also be beneficial [36-44]. Similarly auto-antibodies, and perhaps immunity, can predict development of CHF where there is a family history [45]. Thus an important area that needs to be discussed is the role of environmental and other factors and its ability to alter the course for those who are genetically predisposed. We discuss this subsequently.

GENETIC RISK MODIFIERS OF HEART FAILURE

Unlike inherited cardiomyopathies modifiers of CHF do not contribute directly to CHF but do so in the presence of primary etiologies and in doing so alter the chronology, severity and thus prognosis. In isolation these genes usually have a weak effect. Variation in clinical response or disease progression despite institution of clinical best practice is perhaps the best example [46, 47]. We focus on three important areas where knowledge of these SNP's has shown important clinical relevance.

Single Nucleotide Polymorphisms of Common Counterregulatory Pathways

Myocardial adrenergic receptor blockade is a mainstay therapy for CHF, and dampens the effects of the sympathetic nervous system (SNS). Mean resting heart rates are so critical that for every 5 beat per minute decrease the mortality risk of CHF is reduced by 18% [48]. Polymorphism of adrenergic receptors particularly, the β1 adrenergic receptor (AR), is the most important for cardiovascular hemodynamic modulation. In this regard polymorphism can be toxic by preventing adequate blockade of continuous catecholamine exposure or altering downstream G-protein coupled activity in the absence of catecholamine access. Of the many documented polymorphisms (Box **2**), the 2 most studied are Arg389Gly and Ser49Gly variant [48, 49]. In the former and most well studied, human data shows a gain of function and progression of CHF that can be modulated by ββ. In a study of 2460 patients genetics profiles for β1-AR1 and G-protein receptor kinase 5 (GRK5) responsible to regulating the signal, ββ treatment increased survival in Caucasians but not African Americans. For patients not taking ββ Arg389Gly was associated with reduced survival in Caucasians. GRK5 Leu41 was associated with increased survival in African Americans. All patients with Arg389Gly and GRK5 Gln41Gln polymorphism benefitted from ββ. This study shows that polymorphisms in signaling pathways and not race can contribute to differences in ββ response [49]. In the β-Blocker Evaluation of Survival Trial (BEST) with bucindolol, which also recruited a larger number of African American patients, there was surprisingly no difference between the study group and placebo. Sub-analysis which initially removed African American patients or stratified on genetics, Arg389Arg, revealed fewer adverse outcomes. Retrospective analysis suggested the Arg phenotype which is less prevalent in Caucasians is associated with greater noradrenaline lowering response with bucindolol [50, 51]. This was the first ββ CHF trial to highlight clinical significance for genetic variations. In African American patients the two most important ADRB1 polymorphisms are more common [52].

The second critical feedback factor is the renin-angiotension-aldosterone-system (RAAS) which regulates blood pressure by fluid and electrolyte balance, in heart, kidney and blood vessels through its main effector angiotensin II (AT II), and aldosterone which acts as a potent vasoconstrictor of afferent arterioles and by increasing fluid resorption in distal nephrons respectively. The increased intraglomeruli pressure and salt and water retention contributes to Cardio-Renal-Syndrome (CRS) progression. Along with ββ, RAAS blockade has provided some of the most robust prognostic data for all classes and even prevention of CHF. The ACE gene insertion/deletion (I/D) polymorphism is among the most well studied. Patients with an I/D have higher circulating ACE levels. Prospective follow-up of 328 patients raised clinical correlations between ACE-D allele and, poor transplant free survival. The impact of the D allele does not appear however when treated with ββ [53, 54]. In 479 participants with CHF, the ACE-D allele was similarly associated with increased risk of events. ACE-I and ββ treatment had greatest effect on DD patients, and the D allele effect was blunted by higher ACE-I doses [55]. Several larger studies, with risk factors for CHF, Genetics of Hypertension Associated Treatment (GenHAT) study and Perindopril Protection Against Recurrent Stroke Study (PROGRESS) did not establish causality. A third study on ACE-I treated hypertensive participants showed a 10 year increased mortality risk stratified from greatest risk to lowest risk as DD, ID and II [56]. Similarly a meta-analysis showed that variations for this gene have importance for coronoray artery disease [57], a contributor to CHF. Polymorphism of angiotensinogen (AGT) gene Met235Thr and A1166C of the AII type-1 re-

ceptor contribute to more than 50% in variability of circulating ACE [23, 24]. In a similar Rotterdam study, 4095 participants were investigated for MET235Thr polymorphism of AGT. Subject who took ACE-I with the Thr allele had an increase of myocardial infarction and stroke [58], which were not modified in a subsequent treatment study with ββ [59]. More variations were noted in a Chinese population in risk, genotypes posing risk and response to ACE-I [60]. Perhaps the most important step in RAAS pharmacogenomics was the Perindopril Genetic Association study (PERGENE) of 8907 from which a scoring system using three SNPs could identify benefit or harm with perindopril [61], which highlights a significant advancement in the field [24-26].

Cytochrome P450 System

There is a wide spectrum of response to medications between patients, and genetic factors could account for anything between 20-95% of this. The permutations for this are amplified when we factor in physical characteristics, intrinsic physiological changes with comorbidities and extrinsic socio behavioral characteristics of the patient including diet and other drug use. Genetic polymorphisms of cytochrome P450 enzymes (CYP1B; CYP2 A, B, C9, C19, D6, E, J; CYP4A; CYP 11) could lead to pharmacodynamics or pharmacokinetic factors leading to extremely slow, fast metabolizers and variations in response. In addition there many cytochrome enzymes identified in the heart and their levels are altered during stages of cardiac dysfunction. Enzyme levels in the liver can also be altered by CHF. These systems start having greater relevance when CHF increases severity or with other potential confounders. In these cases adverse drug interactions and events are possible and variations in compliance results. Notable examples are irbesartan, losartan, metoprolol, clopidogrel and simvastatin. The latter two are often prescribed in ischemic cardiomyopathies or when concerns of atherosclerotic risk exist [62-65]. Many ββ are substrates for CYP2D6 enzyme including the CHF class metoprolol and carvedilol. Metoprolol has greater dependency, 70-80% metabolism, for this pathway and patients can be classified as ultraextensive, extensive, intermediate, or poor metabolizers on the inherited number of functional allele. Around 10% of Caucasians are poor metabolizers, where adverse event rates could be as high as 5 fold [66]. Without overstating the effects, as some later studies no significant influence on efficacy or toxicity of drug [52], it is also important not to understate the significance in a regional context with service and monitoring shortfalls, and also where the luxury of low and slow titration is not there, variations may then affect compliance and outcomes. Advancements for several drugs are important examples to highlight. Approximately 15% of clopidogrel undergoes a series of oxidative steps by several enzymes of the CYP450 system to form the active component. In 2208 patients who suffered an acute myocardial infarction, patients with two loss of function alleles for CYP2C19 enzyme had higher event rate (21.5 vs 13.1; HR1.98;95% CI, 1.10-3.58) four times higher rate of a subsequent cardiovascular event following percutaneous coronary intervention [67]. Warfarin is primarily metabolized by CYP2C9. Several genotypes labelled *2 and *3 reduce enzyme activity by 30 and 80%, where homozygote patients require almost similar percentage reduction in maintenance doses. Actual genetic testing to guide dosing is in ongoing evaluation [52, 68].

Modifiers with Direct or Indirect Comorbidity Associations

Cardiac specific SNP's can alter cardiac pathology in the presence of comorbidities and similarly common polymorphism causing disease in other organs (comorbidity) may have relevance for myocardial changes. These points have their greatest relevance for common DCM where the etiology is most frequently coronary vascular disease, hypertension or diabetes. Among 249 patients with renal disease, 40% on renal replacement therapies, there was a significant association between LV mass and Arg389 homozygotes and heterozygotes independent of therapies [69] highlights a case of renal disease accentuating CHF risk. Secondarily are polymorphisms such as those in the nitric oxide pathways that may explain variations in diseases physiology for some groups e.g. A-HEFT trial [70]. As patient populations we are looking after have greater racial heterogeneity this is also important to consider.

GENETICS IN INDIGENOUS AUSTRALIANS

"In the Alice Springs paediatric ward, the vast majority of the 20 or so children are Aboriginal…..For families, a visit to the ward can mean a period of isolation from their community or time with relatives who live in Alice Springs or who also happen to be in the hospital. It may be an unwanted upheaval from relatively peaceful community life, or an urgent and welcome respite from upheavals at home…..The challenge, then, is to balance a paediatric perspective with an Aboriginal one…..We need to find ways through the gaps from several vantage points, with Aboriginal people leading the way back to their own health.

Dr Marcel Zimmet [71]

CHF among Indigenous Australians is underexplored, but accepted to occur at younger ages, more severe, with greater comorbidities and leads to poorer outcomes. Among the most prevalent heritable risks are rheumatic heart diseases, metabolic syndromes, renal impairments and cardiovascular diseases. It is unclear if any single or more SNPs contribute directly, together predisposes or modifies the development of cardiomyopathies. It is also unclear if the susceptibility to conventional risks such as alcohol, cytotoxic agents are modified. Acquired risk factors including cigarette smoking, excess alcohol consumptions and certain recreational drugs are more prevalent. Aspects of CHF in the Aboriginal community have been explored in another publication within this theme [15, 72]. Aboriginal focused cardiovascular genetics research has been lacking. A Medline search '(Genetics, Population/ or Genetics, Medical/ or genetics.mp. or Genetics/)' or '(epigenetics.mp. or Epigenomics/)' or '(Polymorphism, Genetic/ or polymorphism.mp)' and '(indigenous or aboriginal).mp.' reveal 1314 hits. Adding in the search to Indigenous Australians or Aboriginal Australians (Indigenous Australian or Aboriginal Australian).mp. reveals only 19 hits.

Genetic Cardiomyopathies, Risk Factors and Community Differentials

Of the few prospective CHF studies, the Heart of the Heart followed 436 Indigenous adults across six Aboriginal communities in Central Australia. The findings include from this younger chort, age 44±14 years and 64% women were; CHF diagnoses in 5.3% (95% CI 3.2% to 7.5%) when only 35% were previously diagnosed; Asymptomatic CHF cases in 13% (95% CI 9.4% to 15.7%);risk factor prevalence included body mass index (BMI) ≥30 kg/m(2) 42%, hypertension 41%, diabetes mellitus 40%, coronary artery disease (CAD) 7% and history of acute rheumatic fever or rheumatic heart disease 7% [73]. When the authors specifically explored the determinants of disease with an extensive assessment socio-demographic, psychosocial, cardiovascular and metabolic status it was noted that depression increases CVD risk two fold (OR 2.03; 1.07-3.88; $p<0.05$). Residence as remote, peri-urban and urban, contributed differently to risks pf chronic kidney disease (39.7%, 37.2% and 18.2%) and diabetes (28.4%, 34.0% and 19.2%). The glaring findings are increased CHF at young ages, more risk factors with psychosocial and socioeconomic differentials [74].

With significant differentials, and in considering potential genetic variations and their significance it is worth contextualizing on a comment by Gerald Dorn "..is intrinsic human genetic diversity: of ~3 billion bases in the human genome, ~10 million may be expected to differ between any two individuals, in the form of single nucleotide polymorphisms (SNPs), DNA copy number variations (CNV) and rare mutations" [6]. There will be variations for a population separated between 40 -60,000 years, thus suitable strategies for what is collected and how it is interpreted is as important as getting information. Thus whether the factors are described as race based or otherwise it does appear that the population associations and the environment are important for how genes traverse in communities. Starting with inherited cardiomyopathies, we would expect there to be racial differences as would be determined by index cases and subsequent autosomal dominant inheritances within that family and community, and purely by chance There is no evidence however to suggest that Indigenous patients would be more predisposed than any other group. Excess of rheumatic cardiomyopathies are better explained by interactions between poor socioeconomic living conditions and increased genetic predisposition to cross reaction between group A streptococcus and cardiac connective tissues [75].

Sympathetic and RAAS System SNPs

β-AR SNPs are well reported in many populations. Some of these common SNPs are increasingly associated with variable ββ responses: bucindolol – potential genetic due frequency of [52, 76], carvedilol [77], atenolol [78] and metoprolol [25]. It is interesting to note the observations that African Americans may have a poorer responses to ββ and HF outcomes also correlates with may findings of greater prevalence of Arg389 alone and in association with ADRA2C [79] and Leu41Gln variant in GRK5 [49, 80]. Drug specific correlations are also reported as with bucindolol and perhaps carvedilol. With carvedilol data show that Arg389 homozygotes with CHF and atrial fibrillation have deficient chronic heart-rate-lowering response to moderate doses. Importantly the response to one agent need not extend to others, as shown with bisoprolol [81]. In another carvedilol treated HF study, a combination of genotypes had two fold increased mortality [82]. Metoprolol was studied in a South Indian population with β1-AR Ser49Gly polymorphisms. Here SNP altered cardiac response to exercise but not metoprolol [83, 84]. However African Americans were less responsive to metoprolol if they had a GRK4 L65 variant [85]. Several pooled studies have produced data with recommendations that Gly389 allele posed a risk for East Asians but protective in whites and Arg389 homozygotes has a significant association with positive ββ response however treatment with bucindolol and metoprolol could negatively impact survival and left ventricular ejection fraction [86, 87].

The RAAS are important contributors of CHF in Aboriginal patients. The RAAS role starts in-utero where fetal or placental insults lead to reduce nephron numbers. Systemic and intrarenal RAAS further contribute by promoting tubulointerstitial fibrosis. Higher preterm births, lower preterm weight and 404,000 fewer nephrons are realities in this community [88, 89]. The ACE gene insertion/deletion (I/D) polymorphism is at very low frequency of 2% in Australian Aborigines but occurring in 14% of Aborigines with ESRD, and higher incidences of albuminuria [90]. As a whole genetic polymorphisms in the RAAS system can contribute to different renal phenotypes of which there are many variations across racial/ethnic groups which can also then account for variations in renal function [91]. Other potentially significant SNPs include the TT genotype of A240T (rs4292) with 52.3% versus 13.7% in Caucasians, which is located in the promoter region and with increased ACE levels [88, 92]. Idiosyncratic factors like ACE-I induced cough and temperature sensitivity may also have a genetic basis [93, 94].

Are there Racial Differences in Disease Pathophysiology?

There is accumulating evidence of differences in risk factors and even potential pathophysiology in groups of people. The ACE D allele is relatively common in Caucasians and Asians compared to Indigenous peoples, but the proportion of Indigenous patients with the D allele and renal failure is uncharacteristic [88] as is the increased risk for IgA nephropathy in Asians but not Caucasians [95]. Other examples included: a significant elevation of the CV risk factor apoE4 allele in 155 Indigenous compared with 113 European patient's [96], a lipid cluster also noted in Tibetan Aboriginals [97]; inheritance for a robust inflammatory response [95], where previously cardiac antibodies were shown to predict DCM development [45]; novel susceptibility genes in chromosome 3 and 8 where diabetes is six times the general prevalence of 7.5% [96]; and other differences as highlighted by migration and isolation [98-101]. To highlight clusters in communities, the Amish community of Caucasian Dutch origin, the SNP (rs220741) for cardiac hypertrophy gene was noted to contribute to a more progressive form of CHF [102]. Differences can also vary within races. Warfarin, which is required for atrial fibrillation with rheumatic or other cardiomyopathies, is metabolized via polymorphically expressed CYP2C8 or CYP2C9 enzymes, that demonstrate intra-ethnic differences among Chinese, Japanese East and South Asians, and also Caucasians from Europe or America,

altering dosing [103], where other variations are also being discovered [104].

Specifically on pathophysiology of disease it was the hypertension trials which noted differentials in Caucasians and African Americans that started the impetus for a large body of work. Study findings went on to highlight how polymorphisms affected the interplay of systems such as RAAS and pathways such as nitric oxide. CHF excess in African Americans was initially associated to greater risk of hypertensive disease and later to a more complex interplay of factors [105-108]. Coinciding with understanding of a variant etiology for hypertension, studies like African-American Heart Failure Trial (A-HEFT) noted a distinctive benefit with vasodilators in CHF and in ALLHAT diuretics in hypertension [105-112]. From the A-HEFT study, 352 participants enrolled in the Genetic Risk Assessment of Heart Failure (GRAHF) sub-study NOS3 polymorphism, was statistically different to Caucasians, and influenced blood pressure and left ventricular remodelling [70]. In Tibetan Aboriginals two genes NOS3 and ADD gene polymorphisms were associated with hypertension and the later among women particularly [113]. Similarly β1-AR polymorphism can affect LV remodeling, and both of these are more common in African Americans [114]. Among 3863 Swedish hypertensives eight novel blood pressure associated SNPs, showed no pharmacogenetic interactions for BP reduction with ββs, diltiazem or diuretics [115], while others SNPs did [116]. These differences in findings have led to guideline writers factoring genetic information, physiology with clinical findings for improvements to guideline based algorithms.

Heart Failure in Pregnancy and Epigenetic Considerations

Variations in phenotypes can be expressed and heritable regulated through modification of chromosomal components without alterations in the nucleotide sequence. Gluckman et.al has presented strong arguments for developmental plasticity citing examples in the obesogenic environment. Maternal and paternal inherited epigenetic changes, coupled with prenatal cues and neonatal environmental exposures could ultimately determine the risk of developing unfavorable adult phenotypic expressions [117-119]. Structural cardiac changes such as LVH and LVF through modulation of fetal genes and suppression of adult genes requires gene reprogramming that is potentially transmissible [21, 120-122]. For mother's rheumatic heart diseases and predispositions in developing peripartum cardiomyopathies, place risks on the child and mother and for future pregnancies [123-125]. For children programming starts early with higher incidences of low birth weight, preterm delivery, infection exposure and higher risk cardiovascular pregnancies [88]. This is a complex area that also requires consideration in longer term planning particularly in developing a mechanism to monitor patients.

TRANSLATING KNOWLEDGE INTO CLINICAL PRACTICE

"plus ca change, plus c'est la meme chose—the more things change, the more things stay the same".

French Saying

There is an increasing pool of information on genes specific for CHF and those contributing to its risk. There are however permutations in interactions for which the clinical patterns are not always obvious. Thus genetics for CHF is a field where scientific advancements and clinical correlations have not often occurred at the same pace. There are some important points we can consider when looking to contextualize this for the populations we are looking after (Box **1**):

Box 1. Four stages of Genetic Research for CHF in our Region.

Stage	Strategy
Stage 1 HF risk	• Are there potentially significant acquired or inherited genetic confounders in the CHF clientele? • Is it greatly modifiable by optimizing current guideline based care?
Stage 2 Markers	• Are there simple means to identify the population at risk and is the evidence base robust? • Are new markers required? • Are these markers to identify an existing pathology or predict risk of future pathology?
Stage 3 Modulators of Cardiac Impairment	• Are there potential confounders to positive outcomes should pharmacological therapies be delivered effectively? • Are genetic polymorphisms a reasonable consideration?
Stage 4 Future Generations Risk	• Are there system wide risks to patients and their community? • Are these genetic and if so Mendelian Inherited or acquired inheritable?

Importance of Clinical Correlations – Inference or Knowing?

Several models for studying inheritance of CHF including genome wide analyses from a cohort or population studies correlating clinical findings to subsequent genetic studies have both contributed to the area. Genome wide association studies have shown: in 1179 DCM and 1108 controls two new polymorphic [126]; in 200,000 hypertensive of European descents highlighted sixteen novel loci from which a genetic risk score which correlated with phenotypes was derived [127]; in a multidisease study of 2,000 individuals with one of 7 major diseases and 3,000 controls, 24 independent susceptibility sites conferring risk with were identified [128]. In population from the cohort in the Framingham study a hereditary bases for the CHF risk LV hypertrophy and mass was inferred [129]. This association was inferred to be greater among African American than Caucasion patients in the Hypertension Genetic Epidemiology Network (the HyperGEN) study with 1664 participants [130]. Among 445 American Indian families and 1373 participants a substantial proportion of the difference of left ventricular dimensions and mass was inferred to be heredity [131] pointing further to racial for cardiac structural changes. Attempts to identify genetic variants 12,612 participants of purely European an-

cestry, 5 loci harboring common variants associated with LV diastolic dimensions and aortic root size could only explain a very small proportion of difference [132]. Targeted studies in African American following on earlier inferences identified KCNB1 and NCAM1 as contributors to LV structural changes [133, 134]. Finally population data from the Framingham study inferred that excess alcohol consumption is a risk and not cause for CHF [135]. These data suggests that there are situations where causation can be inferred through the strength of the association and others where more in-depth knowledge is required.

Personalized Therapeutics for Heart Failure

Clinical medicine is currently practiced using phenotypic information from patients. The fundamentals for personalized medicine are that no two individuals will respond similarly to pharmacological therapies. The clinical significance for both cases arises when the gradient of this difference is noticeably different, when standard guideline based algorithms are applied and thus causing the patient to be at risk of being undertreated or suffering an adverse event [136]. Fortunately this risk is low. Thus genetics for personalizing therapies are still at a distance. Genetics for screening and counselling is now well established. It has a different role and one that is more selective in CHF. This science is also encouraging for the use of prophylactic treatments but on the whole still requires planning on case by case bases. This area is likely to advance further. Obtaining genome wide information as a means to explain physiology or for retrospective correlations is not backed by any current science. The evidence we have presented does however highlight a contextual case for genetics in CHF care for vulnerable groups. What we have also come to understand from the information is that there are weak and strong genes. In the latter the diagnosis is clear, where preemptive treatment is not a cure and counselling may be relevant. In the former the correlation between genotype and clinical phenotype can vary quantitatively, qualitatively, and inconsistently within the entire makeup of the individual. This point highlights again that any such community study must be accompanied by a robust prospective epidemiological study, where there is forensic epidemiological mapping so that the dynamics of gene, environment and treatment can be truly understood and meaningful conclusions derived. From an earlier example we cited polymorphism of NOS3 and β1-AR which could impact on hypertension was studied in different settings but not together. The opportunity to associate several important factors went missing. Thus it would be of value to identify the constellation of high value targets prior to large studies.

Making Sense of Genetics for Heart Failure

As a collective we have not found the best ways to utilize genetics to provide the information we want. Box **2** provides some examples where positive findings can be used to tailor a regional direction. In summation three important points are worth considering:

a. *Cost – effectiveness and value*: If we look at the example from the Indigenous community, the status quo is a situation of polypharmacy, poor follow-up and uncertain risk factor interaction with disease. We are increasingly encountering patients who have disease patterns and response to therapies that seem to vary from the norm. The value of improving on existing risk scoring systems, preventing adverse drug reactions in principle adds value.

b. *Overstating risks*: The interindividual variability in disease risk, pathophysiology or susceptibility to interaction with disease modifier is the start of further differential in the inter-individual variability in response to pharmacotherapy which can be attributed to three main sets of factors: clinical (e.g., age, acquired diseases and body mass index), environmental (e.g., xenobiotic-drug interactions) and genomic (e.g. genetic variants, gene expression level) [137]. Looking at one well studied example, myocardial hypertrophy has a physiological and pathological spectrum from which we have many things to learn [138]. Thus all associations must be rigorously analyzed.

c. *Clear Treatment and Strategic Pathways*: Clinical correlation is the most significant step for cost effective genetic testing. These could be through several stages. In this regard planning to ensure sample sizes, power and correct collaborations so that knowledge translation can be smooth. In regards to some communities implications could have scientific and political policy consequences which could have effects on many unforeseen levels. These issues should be resolved early.

CONCLUSION

In this review we explored why considering genetics is important in some vulnerable groups. The translation of CHF therapies has not benefited all communities equally. Research in this field has also highlighted that some patients could benefit from therapies earlier, where others may not benefit at all. In addition we understand that this information can be represented as risk scores. This evolving field has made its greatest impact for understanding inherited cardiomyopathies, and at this stage allowed for genetic counselling for families. However with increasing knowledge that some communities such as the Indigenous Australians have poorer outcomes despite well-resourced health services, is an argument for widening the pool of knowledge. In this case we accept that increasing knowledge may not equate to immediate improvement in outcomes. However, the potential alone for this science to narrow gaps is an impetus for clinical researchers to initially hasten prospective audits to define potential disease clusters. This will allow for more focused questions to build a genetics program. Eventually it is hoped the combined data from other studies will build a pool of knowledge that will allow us to better plan treatments, with simplicity and enhance patient satisfaction and life expectancy.

ABBREVIATIONS

AB	=	Aldosterone Blockers
ACE-I	=	Angiotensin Converting Enzyme Inhibitor
AT	=	Angiotensinogen
AT I	=	Angiotensin I

Box 2. Genetic Modulation of Important Effectors in CHF.

Effector Gene	Details	CV Risk	Polymorphisms* PHENOTYPE	c:B:A:H (%)	Notes
AT (AGT)	Precursor for AT - I	+	M235T Inc AT levels & hypertension	?	• More studies needed to define importance of variations in serum AT levels & AT II generation
Renin (REN)	Cleaves AT to AT-II	+	Hind III:Bgl 1 Probably adverse	?	• More studies needed to define importance of variations in serum AT levels & AT II generation
AT – I (AGT1)	Precursor for AT - II	+	?	?	• ?
ACE (ACE)	Cleaves AT-I to AT-II Hydrolysis of bradykinin	++	Ins/Del Intron 16 (I/D) 50% variation in serum ACE level	40-48 37-43 58-70	• Tissues ACE up to 2x higher DD>ID • Polymorphism can affect efficacy of multiple RAAS blockers
AT – II (AGT2)	Most potent effector Aldosterone production	+++	Not Know	?	• More studies needed of serum levels and health in some groups to guide future discussions
ATR (AGTR1/2)	2 main receptors	+	A1166 C Treatment resistant HT	25 5	• ATR-Type 2 not well studied • Irbesartan levels could be affected
Aldosterone	Steroid hormone for fluid and BP regulation Potent Effector	+++	CYPIIB2 – key enzyme in biosynthesis ↑LV size/LVH	?	• No know polymorphism of aldosterone gene
NKR (TACR 2)	Neurokinin. No mutation NK-1R. NK-2R probably relevant		Gly231Glu:Arg375His Increase cough	?	• Identify those benefit from ATRA first line
eNOS (NOS3)	Key non-protein regulator of vascular health	+++	Asp298Glu(Glu894Asp?) Unclear – probably not as significant on its own	22 7	• More studies of effects in association with other comorbidities and genetic alterations • Data on endothelial benefits of therapies could be expanded • Importance of psychosocial health on NO could be expanded
β1 (ADRB1)	Inotropy, chrontrophy Apoptosis and myocardial toxicity with prolonged stimulation	+++	Arg389Gly : Ser49GLY Adverse Gain of function: Protective	24-34:12-16 39-46:23-28 20-30:14 31-33:20-21	• Regional prevalence probably worth exploring due to potential impact on CHF outcomes • Potential for lower efficacy of carvedilol not metoprolol. Other agents unclear.
β2 (ADRB2)	Potential cardioprotection	+	Gln27Glu:Gly16Arg Probably adverse	25:39 19:49 9:51	• Unclear if added information here would be a 'game changer' for regional HF care • High prevalence may suggest worth exploring
α1 (ADRA1D)	Vasoconstriction	+	T1848A:A1905G α1a Arg347/492Cys Unclear	46:38 12:70	• Unclear if added information here would be a 'game changer' for regional HF care
α2 (ADRA2C)	Potential cardiotoxicity	+	α2c Del322-325 Probably adverse	4 43	• Potential racial importance when combine with β1 polymorphisms as shown in Black patients.

(Box 2) Contd….

Effector Gene	Details	CV Risk	Polymorphisms* PHENOTYPE	c:B:A:H (%)	Notes
GRK (GRK5)	Potential cardiotoxicity	+	Gln41Leu Protective	2 24	• Potential racial importance with benefits of ββ more marked in some blacks post-transplant
GNBP (GNB 3)	Potential cardiotoxicity	+	C825T Probably adverse	39 91	• Potential racial importance as confounder to treatment outcomes

Myocyte failure leading to chronotropic and inotropic compensation is detected in the renal juxtaglomerular apparatus and adrenergic systems in the brain, adrenal and spinal column. SNS and RAAS chronically lead a cascade of events that increase blood pressure. These combined efforts are directly and indirectly toxic to cardiomyocytes. Adrenergic blockers and RAAS modulators (ACE-i, ARA, DRI, AB) block the effects of effectors with its receptors. Success is primarily related to the ability to bind the receptor. Genetic polymorphism can influence baseline tissue activity or drug efficacy. As the systems are heterogeneous and complex unwanted and unpredictable side effects can occur. It is important for us to explore the degree of diversity that exists to justify using therapies guided by physiological, pharmacodynamic and pharmacokinetic principles. The RAAS system contributes to numerous deleterious effects including hypertrophy, arrhythmias, cardiomyopathy, and CHF. Components of the RAAS system have defined genetic abnormalities that add additional risks. Each pathway directly contributes to CV disease. (+) = more related to specific function. (++) Comprehensive effects including: direct contribution to diseases, symptoms and events (e.g. CHF, arrhythmias, LVH, atherosclerosis); (+++) More significant combinations of above factors, more aggressive progression of disease; A – Asian; AT – angiotensinogen; AGT-1 Angiotensin I; AT II-T2R; AT 11 T1R; B – African American/Black; C – Caucasion; CT – connective tissue; Del - deletion; DRI – direct renin inhibitors; GNBP - Guanine nucleotide-binding protein; H – Hispanic; LV – left ventricular; LVH – left ventricular hypertrophy; ROS – reactive oxygen species; WBC – white blood (Modified from Ref [6, 13, 51, 139]* Polymorphisms often numerous and reported as multiple. If a specific change is presented it highlights the most studied and relevant for the area. ββ focused pharmacogenomics best studied.

AT II	=	Angiotensin II
ATR	=	Angiotensin Receptor
ATRA	=	Angiotensin Receptor Antagonit
ββ	=	Beta-blocker
CHF	=	Chronic Heart Failure
CRS	=	Cardio-Renal-Syndrome
DCM	=	Dilated Cardiomyopathies
DRI	=	Direct Renin Inhibitors
eNOS	=	endothelial Nitric Oxide Synthase
GFR	=	Glomerular Filtration Rates
HCM	=	hypertrophic cardiomyopathy
IDCM	=	idiopathic dilated cardiomyopathy
LV	=	left ventricle
LVH	=	Left ventricular hypertrophy
NO	=	Nitric Oxide
NOS-3	=	Nitric oxide synthase
RAAS	=	Renin-Angiotensin-Aldosterone-Systems
SCD	=	Sudden Cardiac Death
SNSA	=	Sympathetic nervous system activation

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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