2015/2016 Summer Studentship Project Application Form

Send to: Research Office, University of Otago Christchurch, PO Box 4345, Christchurch, by 5pm on **3 July 2015**

Supervisor Information (First named supervisor will be the contact):	
Supervisor's Name and Title(s): Dr Anna Pilbrow, Prof Vicky Cameron	
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Research Category (Choose one category only – to be used for judging the students' presentations):		
Clinical	**Laboratory**	**Community**

Genes that Predict Outcome in Heart Failure

Project Description:

Aim

This summer studentship aims to investigate associations between 3 genetic risk markers and survival (recorded over 3 years of follow-up) in 750 heart failure patients.

We recently conducted a pilot study investigating associations between several genetic risk markers and survival in 450 heart failure patients. We identified 3 risk markers that were associated with poor clinical outcome, independent of established risk factors, such as older age or elevated circulating neurohormone levels. In this project, we propose the summer student will validate these findings in existing samples collected from a larger, independent cohort of heart failure patients.

Background

It is estimated that one in five adults over 40 years of age will develop heart failure[1]. Heart failure occurs when the heart is unable to pump enough blood around the body to satisfy the body's metabolic demands. Common causes of heart failure include high blood pressure, coronary heart disease or a heart attack. However, heart failure is a complex trait with a significant inherited component[2]. Recent genome-wide association studies have identified new genetic risk markers for heart failure onset[3-6] and progression[7, 8], beyond those previously identified in genes that regulate blood pressure. As yet, it is unknown whether these new genetic markers provide additional prognostic information in heart failure patients, independent of established risk factors (for example, circulating neurohormone levels or echocardiography indicies of heart function). This project will address this knowledge gap by determining whether our 3 new genetic risk markers for heart failure predict clinical outcome over 3 years of follow-up, independent of established clinical risk factors.

Method

This project will use DNA samples from patients recruited to the PEOPLE study, a prospective, observational study of heart failure patients from 4 New Zealand centres (Christchurch, Auckland, Middlemore and Waikato hospitals), co-led by Prof Mark Richards, University of Otago, Christchurch and Prof Rob Doughty, University of Auckland. This study was approved by the Multi-region Ethics Committee (MEC/09/11/124) and all patients gave written, informed consent.

All DNA samples to be analysed in this project have been collected and stored. The student conducting this study will use commercial Taqman SNP genotyping assays to genotype heart failure patients for 3 genetic risk markers identified in our pilot study. These include DNA sequence variants at chromosome 3p22 (rs12638540), 10q26.11 (rs2234962) and 15q13.3 (rs2125623). Taqman SNP genotyping assays will be performed in 5µL volumes in 384-well plates on a Lightcycler 480 real-time quantitative PCR system. Genotyping calls for each risk marker will be confirmed by re-genotyping >15% of DNA samples, selected at random.

The student will establish a database of genotype data and patient clinical information, and perform statistical analysis with SPSS software. Associations between genotype and clinical characteristics will be tested with ANOVA and chi-square tests. Independent associations between genotype and

survival will be explored with Cox proportional hazards models with adjustment for established risk factors such as age, gender, ethnicity, previous medical history, prognostic neurohormone levels and echocardiographic indices of heart function. All statistical analyses will be performed with advice and guidance from Biostatistian, Prof Chris Frampton. A p-value<0.05 will be taken to indicate statistical significance.

Significance

Each year in New Zealand, approximately 5,500 heart failure patients experience a total of 12,000 hospital admissions, each lasting 5 days on average[9]. This consumes approximately 2% of the total health budget and is a signficant burden on the health system. By discovering new genetic markers for heart failure, this research may help identify new biomarkers for clinicians identify high-risk patients who could benefit from more intensive treatment. Ultimately this may reduce the number and duration hospital admisssions for heart failure and improve survival in these patients.

References

1. Mozaffarian D, et al. Executive summary: heart disease and stroke statistics-2015 update: a report from the American Heart Association. *Circulation*. 2015;131:434-41.
2. Lee DS, et al. Association of parental heart failure with risk of heart failure in offspring. *N Engl J Med*. 2006;355:138-47.
3. Cappola TP, et al. Common variants in *HSPB7* and *FRMD4B* associated with advanced heart failure. *Circ Cardiovasc Genet*. 2010;3:147-54.
4. Smith NL, et al. Association of genome-wide variation with the risk of incident heart failure in adults of European and African ancestry: a prospective meta-analysis from the cohorts for heart and aging research in genomic epidemiology (CHARGE) consortium. *Circ Cardiovasc Genet*. 2010;3:256-66.
5. Stark K, et al. Genetic association study identifies *HSPB7* as a risk gene for idiopathic dilated cardiomyopathy. *PLoS Genet*. 2010;6:e1001167.
6. Villard E, et al. A genome-wide association study identifies two loci associated with heart failure due to dilated cardiomyopathy. *Eur Heart J*. 2011;32:1065-76.
7. Morrison AC, et al. Genomic variation associated with mortality among adults of European and African ancestry with heart failure: the cohorts for heart and aging research in genomic epidemiology consortium. *Circ Cardiovasc Genet*. 2010;3:248-55.
8. Parsa A, et al. Hypertrophy-associated polymorphisms ascertained in a founder cohort applied to heart failure risk and mortality. *Clin Transl Sci*. 2011;4:17-23.
9. Doughty R, et al. Changing survival of patients with heart failure in New Zealand over 18 years. *Eur Heart J*. 2007;28(Abstract Suppl):296.

Student Prerequisites (eg. Medical Student) if applicable:
None