WELLCOME TRUST CENTRE FOR HUMAN GENETICS

Roosevelt Drive, Oxford, OX3 7BN

SUBMISSION TO OXTREC: SUMMARY DATA

TITLE OF PROJECT

Genetic Susceptibility to Rheumatic Heart Disease in Fiji

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DURATION OF PROJECT

Recruitment, 2 years, September 2012 to September 2014
Genetic studies, 3 years, September 2013 to September 2016

DATE OF SUBMISION

1st May 2012

SUMMARY OF BUDGET

INTERNATIONAL TRAVEL	FJD 11,000
SUBSISTANCE AND ACCOMMODATION	FJD 27,000
EQUIPMENT AND CONSUMABLES	FJD 55,000
RESEARCH SUPPORT STAFF	FJD 59,000
TOTAL	FJD 155,000

PREVIOUS PROJECTS

Dr Thomas Parks, Dr Joseph Kado, Ms Samantha Colquhoun, Prof. Jonathan Carapetis, Dr Andrew Steer. Underdiagnosis of acute rheumatic fever in primary care settings in a developing country.
Published: *Trop Med Int Health.* 2009 Nov. 1;14(11):1407–13
Winner: Fiji Ministry of Health National Health Systems Research Workshop: Most Outstanding Paper, 2009

Dr Joseph Kado, Ms Samantha Colquhoun, Dr Andrew Steer are investigators on multiple other Fiji GrASP Studies. Prof. Adrian Hill has extensive experience of research on genetic susceptibility to human infectious diseases around the world including work in Vanuatu, New Caledonia and Papua New Guinea.

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SUBMISSION TO OXTREC: DETAILS OF THE PROJECT

OUTLINE OF THE PROJECT

Rheumatic heart disease (RHD) and its precursor acute rheumatic fever (ARF) result from an autoimmune response to infection with *Streptococcus pyogenes* (Group A Streptococcus, GAS). A significant cause of morbidity and mortality in the developing world, it is thought RHD accounts for at least 350 000 deaths annually.

Objectives: The aim is to identify genetic variants affecting susceptibility to RHD through a case-control association study using a genome-wide and fine-resolution approach. The specific objective of this project will be to recruit, consent and phenotype patients with rheumatic heart disease and peer-nominated controls, collect blood, isolate DNA and prepare the DNA for genotyping.

Field study: Over the course of eighteen months, 1200 patients from the Fiji RHD Disease Control Registry diagnosed with RHD by echocardiography as well as an equivalent number of peer-nominated controls recruited from the same population will be enrolled, asked to donate a 5 ml blood sample and consented for genetic studies.

Genetics study: Using a case-control association study approach, microarray technology will be used to genotype genome-wide single nucleotide polymorphisms in 1200 cases and 1200 controls. Putative associated alleles will be replicated in a further 1200 cases and 1200 controls both from Fiji and other sites using additional genotyping technology and data combined via fixed-effects meta-analysis. Later, further genotyping and sequencing up to and including whole genome sequencing will be performed on selected samples to provide greater resolution

Implications: Establishing a collection of DNA samples to study genetic susceptibility to RHD is the key first step in renewing efforts to understand the pathogenesis of this devastating and neglected disease process. In doing so our study may further understanding of the complex interaction between human genetics, susceptibility to infection and autoimmunity, and the results might generate new approaches to diagnostics, therapeutics and disease control.

BACKGROUND

Rheumatic heart disease (RHD) and its precursor acute rheumatic fever (ARF) result from an autoimmune response to infection with *Streptococcus pyogenes* (Group A Streptococcus, GAS), a unique example of an autoimmune process associated with a known specific pathogen. Systematic estimates of global prevalence of RHD suggest 15.6 million people are affected with at least 350 000 deaths annually.[1] Echocardiographic screening studies, however, provide evidence that RHD may have been previously under-recognised in the developing world[2-5], leading some to suggest the mortality may be far greater, perhaps over one million deaths annually.[2]

Despite the significant numbers of individuals affected international funders largely neglect the disease.[6] Even amongst neglected diseases it ranks as one of the lowest-funded diseases, having received less than 0.1% of global research and development funding for neglected diseases in 2008.[7] Unsurprisingly, therefore, to date there is a critical lack of understanding of RHD pathogenesis, in part owing to limited application of the latest technologies, which has hampered efforts in disease control, development of novel therapies and progress with vaccines.[8,9]

a) Pathogenesis of RHD

Rheumatic heart disease is thought to occur as a consequence of autoimmune damage to heart valves following exposure to specific streptococcal epitopes.[6] The consensus in the literature is that cross-reactivity between cardiac proteins and antigens of 'rheumatogenic' GAS strains triggers the inflammatory process.[10-14] There remains, however, a lack of convincing reproducible data to support this hypothesis. Significant unanswered questions surround, for example: the role of myosin, a predominantly myocardial rather than valvular protein, which is thought to be the predominant target of autoimmunity[15]; the importance of the so-called 'rheumatogenic' GAS strains, given the greater diversity of GAS in developing countries where RHD is endemic[16]; and the site of GAS infection, streptococcal impetigo as opposed to pharyngitis being the most common streptococcal disease in the communities where RHD is endemic today.[17,18]

b) Prevention of RHD

The overall lack of effective treatments for ARF and RHD mean efforts to reduce disease burden are currently dependent on prevention.[6,15] Currently control of RHD is limited to antibiotic prophylaxis, either primary treatment of GAS pharyngitis or secondary administration of antibiotics for a sustained period to prevent recurrence of ARF.[19] Both strategies have limitations, however, particularly in low resource settings.[15] Although control might be achieved by immunisation there are major challenges: not only does the development of an effective *S. pyogenes* vaccine require broad coverage but also there is also the risk of induction of autoimmunity.[20] To date only one vaccine candidate has reached clinical trials[21]; currently a GAS vaccine remains at least several years away, and a vaccine that is effective and affordable in developing countries is an even more distant possibility.[20]

c) Genetic susceptibility to RHD

In his classic description of the ‘rheumatic state’, Cheadle referred to the ‘influence of the family predisposition'.[22] More recently pooled analysis of twin studies find monozygotic twins of index cases at six-fold greater risk, indicating heritability of

60%.[23] Similarly longitudinal family studies suggest a sibling recurrence risk of approximately 25%.[24]

Significant progress has been made in the last five years delineating genetic susceptibility to diseases of similar heritability, much pioneered by the Wellcome Trust Case Control Consortium[25], including both chronic inflammatory disorders[26] and bacterial disease such as tuberculosis and leprosy.[27] In Crohn's disease, for example, these advances have provided remarkable insight into pathogenesis.[28] Thus, given the need to further understand RHD pathogenesis, research into genetic susceptibility is a priority and the next logical step.[8]

To date little progress has been made in delineating susceptibility loci consistently associated with RHD[29], largely because the majority of studies have been significantly under-powered and used limited, inconsistent case definitions and genotyping techniques. Key to the recent successes in other diseases, however, was not only prudent application of the latest technology but also standardised disease definitions and adequately sized samples, which took advantage of existing cohorts and international collaboration.[25] For RHD this is now possible, large disease registries having become established in the Pacific[30] and elsewhere, and echocardiographic diagnostic criteria recently having been standardised by an international consensus group.[31] With these advances we propose that the application of tools such as genome-wide association analyses and sequencing to RHD and the study of host susceptibility will provide the much needed insight into pathogenesis.[18]

RESEARCH METHODS

a) Aim of the project

The aim is to identify genetic variants affecting susceptibility to RHD through a case-control association study using a genome-wide and fine-resolution approach.

b) Project design

This project has two components, a field study lasting eighteen months to collect samples sufficient for the second component, the discovery phase of a genome-wide association study. This will be followed up by further validation and fine-mapping of putative associations in further cases and controls.

i) Field study

In April 2012 there were 2035 patients on the Fiji Ministry of Health disease control registry, the majority living in small, relatively easily-accessible geographical areas of the Central and Western Divisions of Fiji. Most of these case participants are receiving secondary prophylaxis and are well known to RHD and local health staff. Compliance with three-weekly secondary prophylaxis continues to improve, having risen from 24% in 2005 to 63% in 2009. Furthermore, over 350 doctors and nurses in the country have recently attended Fiji GrASP workshops. There have also been effective media and awareness campaigns.

Over the course of eighteen months, 1200 patients from the Fiji RHD Disease Control Registry diagnosed with RHD by echocardiography as well as an equivalent number of peer-nominated controls recruited from the same population will be

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enrolled, asked to donate a 5 ml blood sample and consented for genetic studies. We will commission disease control registry staff to approach cases on the registry either directly by telephone or via local clinic staff (Figure 1). Patients will be asked to nominate a friend or neighbour (other than a first-degree relative, that is not a brother or sister, mother or father, or child) of similar age, sex and ethnicity with no history of RHD willing to participate in the study, who the research team will invite to participate in the study, a process referred to as peer-nomination. This strategy has been used successfully in studies of tuberculosis in rural China. In order to encourage participation we will offer controls a free blood glucose test at the same time given all adult Fijians are recommended to get a test at least three-yearly (Fiji Islands Ministry of Health, *Non-Communicable Diseases Prevention and Control National Strategic Plan 2010-2014*.).

Either the principal investigator or trained research nurses from the Fiji RHD and GrASP teams will explain the project to both the patient and volunteer. In addition the participants will be given information sheets available in both Fijian and Hindi. We have arranged for translation and back-translation of these documents following their approval by FNHRC and FNRERC.

In addition to recruiting peer-nominated controls we will also recruit additional healthy adult volunteers as 'population' controls. The Ministry of Health in collaboration with Non-Governmental Organisations runs a programme of Outreach Health Promotion and Screening. Working with Dr Josefa Koroivueta we have developed the strategy of recruiting healthy adults as controls during community visits in Suva and the surrounding area. Each Outreach Project might see several hundred patients within a week so providing an excellent opportunity to efficiently recruit large numbers of volunteers. We anticipate our team attending three to four Outreach visits during the next twelve months through which we would aim to recruit 1000 additional controls. Our recruitment procedure would mirror that of the peer-nominated controls and written informed consent would be obtained from each individual before venepuncture. As described above information would be given in groups.

From each case and peer-nominated control we will document reported ethnicity, location of residence and baseline clinical and demographic details including histories of invasive GAS, ARF, post-streptococcal glomerulonephritis, other significant past medical history (e.g. type II diabetes mellitus), and socio-economic determinants (e.g. occupants per room, household income, maternal education status[32]). From 'population' controls we will document only ethnicity, sex and year of birth. Where it is available, however, we will document venous glucose from both peer-nominated controls and 'population' controls. Where inadequate to confirm the diagnosis, we will consent the patients for and perform a further echocardiogram using a field protocol developed by Dr Andrew Steer and colleagues for use in the Pacific.[33] In addition a subset of adult volunteers, provisionally selected from those recruited at the Colonial War Memorial Hospital, Suva, will undergo to provide controls known definitely not known to have disease ('hypercontrols'). We will collect a single 5 ml blood sample from both cases and volunteers which will be stored in EDTA at 4ºC until transport to laboratory facilities at the Colonial War Memorial Hospital and Matiaka House in Suva where they can be stored at -80ºC. Following DNA extraction at Matiaka House in Suva the sample will be split with a portion stored at the Matiaka House in Suva and the remainder shipped to the Wellcome Trust Centre for Human Genetics, Oxford, UK. At both DNA will be used for the proposed genetic studies and retained for future studies related to RHD and streptococcal disease. Transport and disposal of samples will be according to the

protocols established by Fiji GrASP, which has safely transported and processed thousands of samples for previous projects. Remaining biomedical material including discarded blood will be disposed of at Matiaka House using a commercially available decontaminant.

ii) Genetic study

DNA will be extracted from whole blood by an established salting out technique[34] and quantified by PicoGreen (Invitrogen, USA). Following DNA extraction in Fiji the sample will be split with a portion stored at the Colonial War Memorial Hospital in Suva and the remainder shipped to the Wellcome Trust Centre for Human Genetics, Oxford, UK. At both DNA will be used for the proposed genetic studies and retained for future studies related to RHD and streptococcal disease. A microarray such as the HumanOmniExpress-12 BeadChip (Illumina®, USA) or Human ImmunoChip will be used for genotyping. Additional funding is available from the Wellcome Trust Centre for Human Genetics for the use of such microarrays on completion of the sample collection.

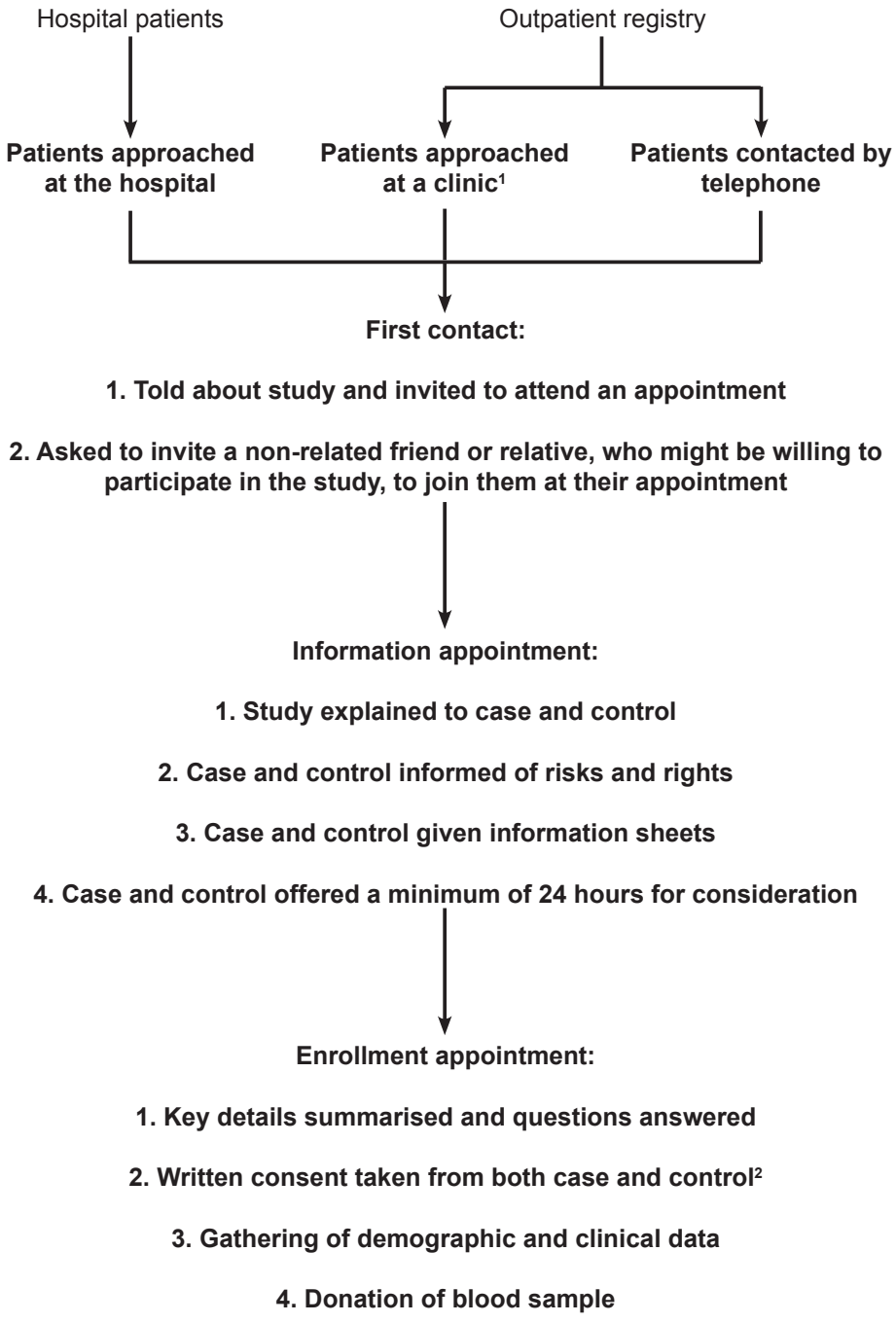
Samples will be excluded on the basis of quality control measures including call rate, heterozygosity, duplication and relatedness. Single nucleotide polymorphisms will be excluded on the basis of call rate, deviation from Hardy-Weinberg equilibrium (HWE) and minor allele frequency. Principal components analysis of identity-by-state relationships between study samples and those from the International HapMap project will be used to remove samples with outlying ethnic background. Components identified in this analysis will also be utilised to adjust for potential population structure and cryptic relatedness. Further to avoid inflation in significance testing caused by population stratification created by inclusion of individuals of Melanesian and Indian ancestry we will use principal components as covariates in analysis.[35] This approach has been successful employed in analysis of African populations with substructure of far greater complexity.[36,37]

Quality control and subsequent statistical analyses will be performed using the PLINK software. Case-control association will be tested using logistic regression, adjusting for components of population structure and any other potential confounding factors as covariates. In order to improve coverage and power, the IMPUTEv2 software will be used to impute variants not present on the HumanOmniExpress, but present in the 1000 Genomes project.[38] Imputed SNPs will be analysed using the SNPTEST software, with adjustment for covariates as above.

Subsequently the 300 most associated, statistically independent SNPs will be followed-up with genotyping in a further 1000 cases and 1000 controls using technology such as Sequenom's MassArray primer extension assay.[39] Again, single nucleotide polymorphisms and samples will be assessed for quality in terms of call rate and deviation from HWE and association analyses performed in PLINK as above. We anticipate recruiting these further patients in Fiji as the disease control registry expands to other population centres, and in addition we will genotype the most significantly associated SNPs in cases and controls recruited at other sites, primarily a study of very similar design set in New Caledonia aiming to recruit a further 1000 cases conducted by our group with the assistance of Dr Mariana Mirabel, Institut National de la Santé et de la Recherche Médicale, Paris France (funded by Dr Thomas Parks' Medical Research Council (UK) Grant (G1100449/1). In addition we will follow-up associated SNPs in a study in the Northern Territories, Australia, expected to recruit 500 cases from Indigenous Australian populations

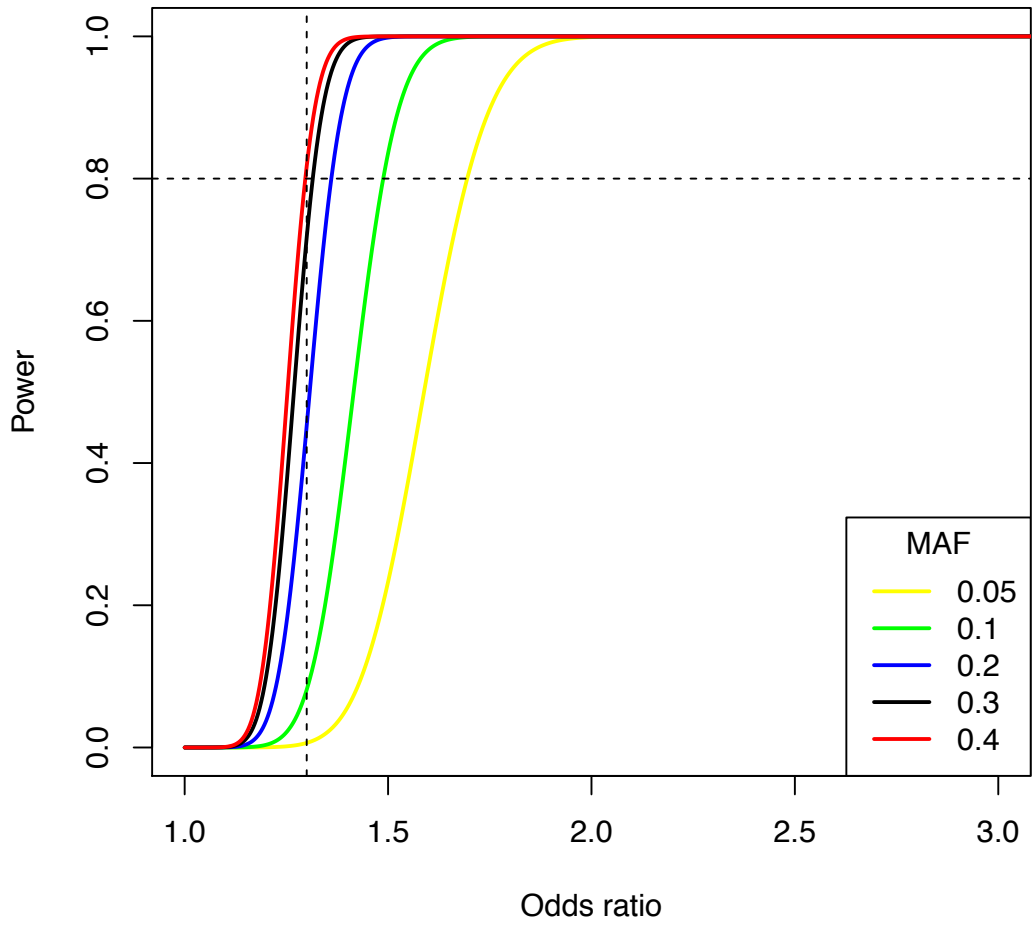
(Prof. Jonathan Carapetis, Dr Andrew Steer and colleagues, funded by the Australian National Health and Medical Research Council). Thus, at the completion of the discovery and follow-up stages of the study we would anticipate a total of over 2200 cases and 2200 controls which will be combined via fixed-effects meta-analysis. If a causal variant (or a SNP in complete linkage disequilibrium with a causal variant, r^2 = 1) is genotyped in both stages the cohort will give over 80% power to detect significant association at allelic odds ratio of 1.3 or greater for alleles with a minor allele frequency of 30% or more at genome-wide significance (p-value = 5×10^{-7}, Figure 2).[25] Later, further genotyping and sequencing up to and including whole genome sequencing, particularly comparison of extreme phenotypes (that is those RHD patients with most severe disease against hypercontrols known to be disease free) will be performed on selected samples to provide greater resolution.[27] Finally meta-analysis with other group A streptococcal disease phenotypes such as invasive group A streptococcus and potentially other infectious disease phenotypes will insight into the relevance of putative associations to pathogenesis.

Figure 1. Recruitment and consent process



[1]The majority of patients will be recruited through routine follow-up such as administration of secondary prophylaxis.
[2]At enrollment we will take informed consent from the case and control separately. In order to prevent coercion, a decision by one not to participate will not preclude the other.

Figure 2. Power calculation for 2400 cases and 2400 controls



IMPLICATIONS

We propose that a large, well-designed study employing a genome-wide approach will provide an important insight into the biology of the RHD as has been demonstrated in other common human diseases.[25] While the Wellcome Trust Case Control Consortium and others have taken advantage of existing large-scale collections of DNA, such sample sets do not yet exist in RHD[18], where genetics research has to date been characterised by studies of poor quality, the majority including less than 100 patients.[15,29] For us to pioneer studies of genetic susceptibility to RHD, the crucial first step is to establish similar large collections of well-phenotyped patients and it is logical to do so in a setting such as Fiji where the disease is endemic and a major public health problem in the context of an established control programme.

Rheumatic heart disease is a unique example of an autoimmune process associated with a known specific pathogen. Therefore, with the potential to reveal genetic variation associated with susceptibility RHD, this study might further our understanding of the complex interaction between human genetics, susceptibility to infection and autoimmunity. Further, insight into RHD pathogenesis gained through

studies of genetic susceptibility has significant potential to inform efforts to develop reliable diagnostic tests, therapeutics and vaccines. For example, genetic susceptibility to infection is being pursued in the hope that it may have a major impact on vaccine development, as earlier studies of genetic susceptibility to malaria have shown.[40,41]

TIME FRAME

We will ascertain cases, sample blood and extract DNA between September 2012 and January 2014. Genetic analysis will begin towards the end of 2013 and will continue until September 2016. Following completion of the proposed study, we will retain DNA and genetic data for use in further studies for which ethical approval would be sought.

FUNDING

A Medical Research Council (UK) Grant (G1100449/1) will pay the Principal Investigator's salary, subsistence and accommodation. The British Medical Association Josephine Lansdell (2012) grant awarded to the Principal Investigator for £44,850 (FJD 126,400) will pay the remainder.

DETAILED BUDGET

TRAVEL	
INTERNATIONAL TRAVEL	**FJD 11,000**
EQUIPMENT AND CONSUMABLES	
VOLUNTEER AND CASE REIMBURSEMENT	FJD 10,000
SAMPLE SHIPMENT TO UK	FJD 14,000
VISA AND PERMITS	FJD 1,000
REGISTRY AND ECHOCARDIOGRAPHY COSTS	FJD 5,500
LOCAL TRANSPORT (FUEL)	FJD 3,000
LOCAL TRANSPORT (VEHICLES)	FJD 2,000
DNA EXTRACTION	FJD 6,600
DNA QUANTIFICATION	FJD 3,400
VENEPUNCTURE EQUIPMENT	FJD 9,500
SUBTOTAL	**FJD 55,000**
RESEARCH SUPPORT STAFF	
RESEARCH ASSISTANT SALARIES (CLINICAL) EQUIVALENT TO 2 YEARS FULL-TIME EMPLOYMENT	FJD 60,000
SUBSISTANCE AND ACCOMMODATION	**FJD 27,000**
TOTAL	**FJD 153,000**

ETHICAL CONSIDERATIONS

a) Confidentiality, storage and access to data

Only the local research team in Fiji will know the names of the participants. Once dispatched from the research site each sample and data sheet will be allocated a unique index number such that researchers will not be able to identify participants.

Consequently the results of genetic studies will not under any circumstances be conveyed to the participant.

Data will be entered into an electronic database. The original datasheets will be stored in a locked repository and retained for five years. The electronic database will be password protected and only individuals directly involved in the project given access. The custodian of the data will be Dr Thomas Parks at the Wellcome Trust Centre for Human Genetics, and the rest of the study team including Dr Kado in Fiji.

Following completion of the proposed study, we will retain clinical and genetic data as well as samples indefinitely for use in further studies related to group A streptococcal disease and RHD as outlined in Section 5 of the consent form. In addition de-identified data will be made available following publication through the European Genome-phenome Archive, as required by many research funders, and researchers will be able apply to access the data providing their project is approved by FNHRC as outlined Section 6 of the consent form.

b) Cultural aspects of research

While all cultural groups living in Fiji will be offered the chance to participate in the research there are specific cultural considerations to the conduct of the genetics research in populations in developing countries and indigenous peoples.[42] Notwithstanding a difficult history of biomedical research in these settings characterised by unethical practice, which has lead to a break down of trust between research and the communities[43], we believe it is vital that the populations of developing countries have the opportunity to participate in genetics research particularly given the excess burden of disease and the potential of genetics to assist improvements in diagnostics, prevention and treatment. The extension of the Human Transition Projects to Fiji in collaboration with Georgia Technical Institute (the first population based genetics study in Fiji, http://www.gibsongroup.biology.gatech.edu/human-transition-projects) serves as an example of increasing efforts to engage populations in developing countries in genetics research.

In the proposed study we are privileged to follow in the footsteps of the Fiji GrASP project which has enrolled thousands of children and adults to studies of Group A Streptococcal disease mostly in the Central and Western Divisions of Fiji. These studies, conducted in close collaboration with the Ministry of Health, have helped to promote awareness of research. Much has been learnt about how to achieve valid consent in the local population which can be applied to the proposed study. Further these have facilitated mutual respect and trust between researchers and communities. Crucially these studies continue to address diverse priorities in group A streptococcal disease research of which RHD pathogenesis is just one component. We believe, however, that improvements in our understanding of RHD pathogenesis would have the potential to bring benefits to the population of Fiji, the prevalence of RHD in some communities in Fiji and other Pacific island nations exceeding that anywhere else in the world. Working with the Fiji GrASP project we will work to convey the results of the studies both to health professionals and the communities involved in the research. Further Fiji GrASP continues to be involved in work to build research capacity in Fiji and the proposed project will provide opportunities for Fijian researchers to gain experience of genetics research which can be translated to other diseases.

In order to reach valid conclusions about the link between disease and genes it is necessary to understand the genetic make up of the population being studied and make comparisons both within the participants and with other populations around the world. This might include, for example, comparison of the relatedness of Indo-Fijian people and Indian peoples living in the Indian Subcontinent or the relatedness of the Indigenous Fijians with peoples elsewhere in the Pacific. We emphasise that we will do these analyses as a necessary step in the understanding the genetic determinants of RHD and not to gain insight into the history or anthropology of the peoples of Fiji. Further the study of genetic differences between populations can be useful and was, for example, a necessary step in the lead up to genome-wide associations.[25,44,45] To date Pacific Islanders have largely been left out of these studies. Thus in the scenario that our analyses lead to findings about the genetics of the peoples of Fiji which are irrelevant to RHD or group A streptococcal disease but which we think merit publication in peer-reviewed journals because they are likely to be useful to the global scientific community and lead to benefits for human health we will seek permission of the Fiji National Research Ethics Review Committee to present or publish these data.

c) Informed consent

All volunteers will receive written and verbal information and careful counselling prior to participation in the study with specific reference to use and storage of DNA, and inclusion of genetic data for further studies in a public electronic library. Written consent will be collected from each participant on individual consent forms prior to donating blood. Each sample and data sheet will be allocated a unique index number such that the researcher will not be able to identify participants. The results of genetic studies will not, therefore, under any circumstances be conveyed to the participant.

Issues relating to consent for genetics studies in developing countries have been considered previously.[46,47] We have reviewed the implications of the key issues for the proposed study in Fiji:

i) Disclosure and comprehension of information

While Fiji GrASP has increased awareness of research we anticipate the majority of the population will know little of human genetics despite Fiji's rating in the 2011 United Nations Human Development Report's Educational Index (0.786 compared to 0.715 for High Human Development nations). To address this all participants will attend an information appointment with a research nurse at which the project will be explained in detail without jargon as outlined above. We have modelled consent forms and participant information sheets on those used successfully by Fiji GrASP for the last five years adapting them for this project with the input of our team of local research staff.

ii) Voluntariness

Access to the provision of health care in research projects in resource-poor settings has been highlighted as a reason participants feel pressured to take participate in research. The crossover of research staff and procedures (e.g. echocardiography and venepuncture) with routine clinical care compounds this situation. In the proposed study, however, we emphasise that participants will be recruited from the registry, rather than directly from the community. Thus they will have already

obtained access to healthcare before considering taking part in the research. We will also underline the distinction between healthcare and research (through repetition and comprehension assessment during recruitment) and highlight the participants right to withdraw during the enrolment process.

To encourage participation of peer-nominated controls we will offer a blood glucose test when they attend for there blood test. Our strategy for testing will mirror that of the Fiji Islands Ministry of Health and World Health Organisation. We emphasise our testing is not a formal screening programme but instead simply provides an additional for earlier diagnosis. For a well-publicised disease we suggest that the opportunity to have blood glucose checked at the same time as giving a blood sample for the study will encourage volunteers to participate but, given the availability of testing from the Ministry of Health, is highly unlikely to be unduly inducing. It is also consistent with Ministry of Health campaigns to promote active case-finding in at risk individuals.

iii) Competence

For consent to be valid it must be given competently which can be problematic in specific vulnerable groups of the population. To avoid difficulties we will exclude any individuals unable to give informed consent for any reason including severe illness or learning difficulties. Recruitment of children will mirror the Fiji GrASP procedures whereby we will require third party consent for children aged five to nine years, third party and child assent for children aged ten to fifteen years and independent consent for all those aged sixteen years or more.

iv) Consent for the future use of genetic information

Our participant information sheets specifically outlines both the indefinite storage of samples for further studies and inclusion of electronic data in databases for use by other researchers with permission. We will stress, however, that it will be impossible for the researchers to link information about the participant, genetic data or their sample back to the individual.

v) Community dimensions of consent

In many communities there is greater on familial or communal dimension of decision-making with greater emphasis on community gatherings, group discussions and consultations. Fiji GrASP has worked with communities in developing research over the last eight years. We will continue this process for the proposed project. In addition we will emphasise to individual participants the scope for them to discuss their decision to consent to the study with partners, family, neighbours, colleagues and other members of the community. To promote such discussion participants will be offered a minimum of twenty-four hours deliberation time between the information appointment and enrolment.

c) Clinical Assessment

In the clinical assessment of participants we may discover something about their health that is useful for that participant and their doctor to be aware of. Where we have access to inadequate echocardiographic data, cases will undergo echocardiography. The result, which will reveal detailed information as to the severity of rheumatic heart disease (RHD) and the risk of complications, will be conveyed,

with the patient's consent, to the doctor responsible for their care. We anticipate that this data will be of considerable value for follow-up and treatment decisions but given the cases will be ascertained from an established RHD programme such data should not place an additional burden on local healthcare resources. If a new diagnosis is identified as part of the clinical assessment the patient's doctor will also be informed. Such findings might range from skin disease noted in the clinic room such as streptococcal pyoderma, frequent amongst patients with RHD in the Pacific, to an unexpected finding at echocardiography such as congenital heart disease, in which case referral to local expertise will be recommended.

SAFETY

The only risk to participants is that associated with phlebotomy, which may result in mild tenderness, bruising, light-headedness or rarely vasovagal syncope. There is no risk from echocardiography.

CONSENT FORMS AND PLAIN LANGUAGE SUMMARIES

There are three consent forms in use in this study dependent on age:

Age	**Consent**	**Form(s)**
≥ 16 years (adult)	Independent consent	1
10 - 15 years (child)	Third party (parental or guardian) consent AND child assent	2 AND 3
< 10 years (child)	Third party (parental or guardian) consent	3

There are five plain language summaries (PLS) for specific groups:

PLS	**Target audience**
1	Adult Patient Participant
2	Adult Healthy Volunteers
3	Child Patient Participant (information for parents or guardians)
4	Healthy Child (information for parents or guardians)
5	Information for children (aimed at children aged 10-15 years)

All these documents will be available in Hindi and Fijian. We have arranged for translation and back-translation of these documents following their approval by FNHRC and FNRERC.

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