Lessons learned in genetic research with Indigenous Australian participants

Genetic research with Indigenous Australians is achievable with community engagement and appropriate governance mechanisms in place

Steven YC Tong[1,2]
Heather D'Antoine[2]
Melita McKinnon[2]
Kyle Turner[1]
Maui Hudson[3]
Ngiare Brown[4]
Jonathan R Carapetis[5]
Dawn C Bessarab[6]

1 Victorian Infectious Disease Service, Royal Melbourne Hospital, and Peter Doherty Institute for Infection and Immunity, Melbourne, VIC.
2 Menzies School of Health Research, Darwin, NT.
3 University of Waikato, Hamilton, Waikato, New Zealand.
4 South Australian Health and Medical Research Institute, Adelaide, SA.
5 Telethon Kids Institute, Perth, WA.
6 Centre for Aboriginal Medical and Dental Health, University of Western Australia, Perth, WA.

steven.tong@mh.org.au

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The importance of including minority populations in research is increasingly recognised.[1] Advances in clinical and research genomics have highlighted the need for and challenges of inclusion of Indigenous populations in genomic studies.[2,3] Previous negative experiences in genomics research in Indigenous populations[4,5] have placed substantial barriers, but the opportunity now exists to take a fresh approach through genuine partnership with, and leadership from, Indigenous communities and their representatives. In this article, we reflect on the lessons learned from a recent genome-wide association study of rheumatic heart disease (RHD) with Aboriginal Australian participants.[6]

The term Aboriginal will be used when referring to communities and participants in the study. Indigenous will be applied when referring to the broader national and international context and research methodology.

Our aim here is to add value to what is considered best practice in genetic research with Indigenous peoples and place our experience in the context of international standards. We provide some practical recommendations for other researchers in what is a complex and sensitive area.

RHD is an acquired cardiac disease following recurrent episodes of *Streptococcus pyogenes* infections. In the Northern Territory, the prevalence of RHD among Aboriginal children aged 5–14 years is up to 1500 per 100 000.[7] Despite almost universal exposure to *S. pyogenes*, most Aboriginal people do not develop RHD. We sought to determine whether there are genetic differences between those with and without RHD. Our study included 398 Aboriginal people with RHD (cases) and 865 Aboriginal community-matched controls across the NT. Variation at a genetic locus connected with the immune response (HLA_DQA1-DQB1) was associated with RHD.[6]

The study was overseen by a project steering committee and three subcommittees — Aboriginal governance, clinical and scientific. The chief investigators included three Aboriginal researchers, four clinician researchers and two geneticists who were not Aboriginal. The Aboriginal Governance Committee (AGC) comprised eight members, the three Aboriginal chief investigators, three Aboriginal community-based researchers, an independent Aboriginal researcher and a Māori researcher. The AGC had direct input into the study protocol and the right of veto over any key protocol changes. The AGC provided guidance to the day-to-day project team. In turn, the project team informed the AGC of how the project was progressing and what needed to be adapted. This reciprocal working relationship was critical to the project.

Stage 1 of the project involved community engagement and consent, development of culturally appropriate consent materials, and the establishment of governance protocols for the collection and storage of samples. Stage 2 involved identifying participants, a free, prior and informed consent process, and the collection of samples and metadata. Individual consent was an opt-in process. Participants selected which components of the study they would participate in, including consent for future use of samples and data. Participants were able to withdraw from the study at any stage.

The participants were recruited from 19 communities. Of 1641 potential participants screened, 1371 (84%) consented to participate. Of these participants, 722 (53%) requested that data and samples not be used for future research; the remainder consented to future research related to either RHD or other Aboriginal health issues (n = 500, 36%), only RHD (n = 139, 10%), or only other Aboriginal health issues (n = 10, 1%). We noted that people or families without RHD were less interested in participating, while those with RHD who declined to participate were either too busy or just not interested.

After the study completion, we explored what worked well and what could have been done better. We developed a nine-point questionnaire for research team members, which included investigators, AGC members, project staff, and research fellows. Responses were provided by 12 of the 14 people approached. Questionnaire responses were collated and a general inductive approach and thematic analysis was performed by an Aboriginal post-doctoral researcher not involved in the RHD study. Key themes were generated from recurring patterns of responses and summarised as recommendations for future genetic research (Box).

Recommendations for future genetics research with Aboriginal Australians as generated from a thematic analysis of survey responses following a rheumatic heart disease genetic project

Recommendation	Example of survey response
1. Strong and ongoing community engagement is paramount	• "The importance of keeping community involved, and ensuring that they understand the research and become key stakeholders"
2. Plan for a lengthy engagement, informed consent and recruitment process	• "The importance of the preparatory work before ensures that solid foundations are laid to conduct a complex study such as this. Inviting a number of people, particularly Indigenous people, to be involved in the conversation about the pros and cons of doing a genetic study and how we might go about it" • "We had time to think"
3. Borrow on the strengths of Indigenous understandings of the basic principles of genetics and genetic research, and their enthusiasm to learn more	• "Aboriginal people know a lot more about genetics than we (I) realised and I am Aboriginal. The Aboriginal kinship is based on genetics. I think we should have used Aboriginal words when conducting the yarning circles. Instead of starting with words like 'genetics' and 'DNA' which are western words, we should have used words like 'kinship system' and 'skin groups'" • "Indigenous people are keen to partner with scientists to learn more about their own history and genetics"
4. Aboriginal leadership should be visible across every line. Consider forming an Aboriginal Governance Committee (AGC) with the right to veto	• "It was important to decide from the start that the ethics and governance component was equally important to the science component … and to pull together the AGC and offer it right of veto" • "Aboriginal people must be involved in the research. Aboriginal people must have ownership and provide governance to the research"
5. Ensure clear, regular and, ideally, face-to-face communication among the multidisciplinary team	• "More full team face-to-face meetings early on, and during, the project. I don't think that teleconferences work that well"
6. A formal staged process for study development provides space for achieving milestones before embarking on the next stage, and should include planning for post-project data storage and access	• "For Stage 1, the discussions that occurred in the AGC meetings were very rich and informed the consent process as well as how to manage the data after this project ended"

The Universal Declaration on the Human Genome and Human Rights, ratified in 1997, highlights the importance of prior, free and informed consent for research participants (Article 5b), and that "No research or research applications concerning the human genome, in particular in the fields of biology, genetics and medicine, should prevail over respect for the human rights, fundamental freedoms and human dignity of individuals or, where applicable, of groups of people" (Article 10).[8] For Indigenous peoples around the world, there should be particular acknowledgement of rights, participation and respect for the integrity and safeguarding of social, cultural, religious and spiritual values.[9] These two documents provide an important framework for the conduct of genetic research with Indigenous peoples.[8,9]

Unfortunately, these principles have not always been adhered to. Previous genetic research with Indigenous peoples have led to concerns about racial stereotyping, cultural undermining, genetic theft, the potential for genetics to be used to define Aboriginality, lack of benefit to communities, diversion of attention and resources from non-genetic causes of health, and misuse of samples.[1,10]

These issues have acted as a significant barrier to conducting genetic research with Indigenous Australian communities. However, the past 10 years have seen several studies investigating genetic associations to diseases with high prevalence among Indigenous Australians: kidney disease,[11] otitis media and diabetes,[12] vulvar cancer,[13] and RHD.[6]

Experiences from the conduct of such studies can be reflected on in the context of the above mentioned principles of prior, free and informed consent, respect for human rights and dignity, and the social, cultural, religious and spiritual values of Indigenous peoples.

Ongoing community consultation and engagement (Box, recommendation 1), embedded from the beginning in our study aims, timelines and budget, were critical to allow informed consent at the community level. For a complex genetic project, such engagement took time (Box, recommendation 2) — patience was appreciated by the study participants, community leaders and the AGC.

At the individual level, participants already had a good understanding of genetic principles (Box, recommendation 3). An Aboriginal investigator noted, "Aboriginal kinship is based on genetics". Once the information and consent processes were completed, most individuals were happy to participate. However, a significant proportion of participants (53%) did not consent to the future use of samples and data. It was not clear whether this reflects an appropriate level of informed consent and willingness to decline participation in aspects of the study or, alternatively, that the study did not adequately explain the value of future use. Either way, we could have better valued existing Aboriginal knowledge by using Aboriginal words in our explanation of genetic concepts (Box, recommendation 3).

Respect of the rights of Aboriginal communities and individuals, and their cultural and spiritual values, is only possible with Aboriginal leadership and participation. We established a management structure to reflect this leadership (Box, recommendation 4). As team members were geographically separated, many meetings were held by teleconference. We would have benefited from more face-to-face meetings earlier on to improve communication about complex concepts and to cement team relationships (Box, recommendation 5).

There were two instances where the AGC did not endorse proposed substudies. One involved an external group requesting the use of participant DNA for whole genome sequencing. The other was for a study investigating population genetics and ancient population movements. These studies were thought to be outside the study purpose and scope stated during the informed consent. These decisions were relatively straightforward to make, given the clear parameters that had been set at the beginning about the aims of the study, what participants were consenting for, and how decision making would be governed. We suggest that consent should be specifically requested for studies of population genetics.

As the study progressed, it became clear that we needed to prepare for life after the study (Box, recommendation 6). The AGC provided permission to lodge de-identified genotype and basic demographic data (broad geographical location, age, sex and phenotype information) in the European Genome-phenome Archive, with stipulation for use of the data only in health-based research and not for pure population genetics research. We formed a Data Access Committee (DAC) to consider data access requests. The DAC membership includes the heads of Aboriginal research of the two main research institutes (Telethon Kids Institute and the Menzies School of Health Research), a senior research fellow in Aboriginal health, geneticists and heads of chronic disease divisions. The AGC granted the DAC the capacity to approve requests to access data without the need to return to communities for permission.

Despite the perceived high risk nature of our project, the challenges that arose, and some mistakes that were made, we completed the project with a sense of walking in a culturally safe manner. Genetic research with Indigenous Australians is achievable with the right team and mechanisms in place. Critical elements to the success of the project included the establishment of a multidisciplinary team with strong Aboriginal leadership, an effective project team, growing trust among team members, privileging the Aboriginal voice through the governance structures, preparedness from non-Indigenous investigators to listen and learn from Indigenous colleagues, and taking our time.

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