Article

New insights into ancestry and health of Polynesians and New Zealand Māori

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We are now moving towards the new era of personalised medicine. In prospect, a DNA-tailored healthcare system will utilise genomic information from patients and populations for the prevention and treatment of diseases. This near-future medicine recognises that there is already evidence of genetic disparity between people of different ethnicity. Our own previous genetic surveys of human genomes have demonstrated abundant genetic variation in New Zealanders. These now include extensive new work on immune system genes. We have produced a comprehensive reference set of genotypes for clinically relevant antigens in transplantation (human leukocyte antigen, major histocompatibility complex class I chain-related gene A and killer cell immunoglobulin-like receptor) and transfusion (blood group and human platelet antigens) medicine in Māori and Polynesians. This report sets these data in context and highlights allelic variations and their implications for ancestry and health. It is hoped that this information may help to resolve some of the present inequalities in Māori and Pacific health status.

Introduction

We have been engaged on a programme of medical genetic research for 30 years. This tests the proposition that the genepools of Māori and Polynesians are extensively differentiated from those of Europeans. Further, that these differences are markers of ancestry and medically significant. Many of our earlier reports support this position and we now review an extensive body of new evidence drawn from recently published analyses of immune system genes in these populations.

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Our research programme has its roots in forensic science via establishment of first-generation genetic profiling via DNA fingerprinting (Hamilton *et al*. 1996). From 1988 to 1990 we collected a bank of DNA samples from volunteers in the Wellington area with the assistance of the local Blood Transfusion Service. Samples were grouped according to self-declared ethnic affiliation (the forensic standard definition), but supported with an interview questionnaire to better establish genetic ancestry. This latter feature was to prove of paramount significance for effective use of the VUW DNA Bank for medical genetic applications. Our forensic study confirmed the expectation that Polynesians have lower levels of genetic variation and showed that these levels were even further reduced in Māori (Clark *et al*. 1995). Such initial findings raised concerns about the utility of the then available genetic techniques to build unambiguous missing persons databases. This problem was investigated using mitochondrial DNA (mtDNA) (Whyte *et al*. 2005) and Y-chromosome (Underhill *et al*. 2001) markers. There were two remarkable extension findings from these two studies. First, in our Māori subjects approximately 15% of mtDNA genomes and 50% of Y-chromosomes proved to be of European origin, reflecting the gender-biased pattern of recent historic admixture. However, this also implies that minimally 35% of them are of full Māori descent. Second, the maternal and paternal genetic lineages track back to different geographic origins: Taiwan Aboriginal for mtDNA and Papuan for Y-chromosomes. Again this reflects historic gender-biased geneflow, but set much

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deeper in time. These features are captured by the *Synthetic Total Evidence Model* of oceanic settlement (Chambers 2006).

The medical genetics programme began with a study of alcoholism in young men (Chambers *et al*. 2002). This survey confirmed our expectation that a hepatic alcohol dehydrogenase variant then known as *ADH 2*2* was common in Māori. Coupled with the failure to observe a corresponding aldehyde dehydrogenase variant *ALDH 2*2* linked their nuclear genomes to Taiwanese Aboriginals rather than Han Chinese. This observation is important for our understanding of genetic influences on the health of the wider domestic population. This is because the *ADH 2*2* variant is protective against the onset of alcohol abuse behaviour and very rare in those of European origin. This was followed by a series of investigations of disease susceptibility markers including; Crohn's Disease (Gearry *et al*. 2006) and Metabolic Syndrome (Myles *et al*. 2011), on the pharmacogenomics of drug response (Lea *et al*. 2005, 2008, Lea & Chambers 2007b) and a commentary on the complexities of genotype–environment interactions (Lea & Chambers 2007a).

We are certainly not alone in claiming that advances in molecular biology have shed light on human genome associations with disease pathogenesis. In fact, the whole field of genomics seems to be moving rapidly towards developing personalised medicine. This is now emerging as a real prospect in the prevention and treatment of diseases. Indeed, a fully DNA-tailored healthcare system is one ultimate goal of near-future medicine, as many infectious and autoimmune diseases (e.g. tuberculosis, diabetes, coeliac disease and leprosy) have now been directly linked to human genes (Ghodke *et al*. 2005, Mourant *et al*. 1978, Qidwai & Khan 2011, Stephens 2001, Zhang *et al*. 2012). Molecular approaches point to genetic alterations due to mutation, failure of recombination processes or cellular repair mechanisms. These changes may influence individual susceptibility or resistance towards particular diseases and there is already widespread evidence of genetic disparity between people from different ethnic groups. Genetic surveys of the human genome, including those on immune genes have revealed many differences between genetically and geographically unrelated populations. Most recently our own team has produced a comprehensive reference set of genotypes for clinically relevant transplantation and transfusion antigens (i.e. human leukocyte antigen, major histocompatibility complex class I chain-related gene A, killer cell immunoglobulin-like receptor, blood groups and platelet antigens) in Māori and Polynesians. The following sections highlight the implications of these allelic variations for ancestry and health.

Recent insights into ancestry in Māori and Polynesians

The first question that must be answered is: How did the European and Polynesian genepools become so divergent? The primary answer lies in the early separation of genetic lineages as anatomically modern humans first left Africa (Chambers 2008, 2013). Our presently emergent picture of Polynesian origins is captured by the extended version (Chambers & Edinur 2013, 2015) of the *'Synthetic Total Evidence Model (STEM)'*; see Table 1 for this and other competing models.

According to *STEM*, the distal sources of populations that contribute to the settlement of Remote Oceania can be divided into at least two groups; first an ancient Papuan-speaking Australoid lineage (P-SA; ancestors of Australian Aborigines, ex-coastal Melanesia, hill tribes of Papua New Guinea, Andaman Islanders and Negritos) moved South from Asia 40,000–70,000 yrs ago and the second group of Austronesian-speaking Mongoloids (A-SM) who first occupied Taiwan around 4000–6000 years ago (see Figure 1). The A-SM people migrated to Island South East Asia (ISEA), coastal Papua New Guinea and Island Melanesia between 5000 to 3500 years ago (Bellwood *et al*. 2011, Chambers & Edinur 2013, 2015). In coastal settlements around northern mainland Papua New Guinea and the neighbouring islands, matrilineal marriage meant that numerous P-SA men were recruited by the A-SM voyagers and contributed towards a gender-biased genetic admixture process; see Chambers & Edinur (2013) for further details. The newly formed hybrid population (ancestral Polynesians) then moved outwards to Remote Oceania (Polynesia) and eventually occupied New Zealand from around 750–650 years before present (ybp). Genetic admixture continues today as Māori and Polynesian people intermarry with the descendants of Europeans who arrived in New Zealand over the last 150 years. These historical events have left a 'genetic trail' that stretches from Taiwan to New Zealand, Hawaii and Easter Island.

The general account above, and other recent New Zealand commentators (Gosling *et al*. 2015, Matisoo-Smith 2015), has received independent confirmation from large-scale phylogenetic studies of Pacific and East Asian languages (Gray *et al*. 2009, 2011) and autosomal genes (Friedlaender *et al*. 2008, Kimura *et al*. 2008, Lipson *et al*. 2014, Wollstein *et al*. 2010). The story that developed from analyses of these autosomal markers showed a hybrid A-SM:P-SA origin of Polynesians. They also clarify the enigma arising from works on maternal (mtDNA) and paternal (Y-chromosome) markers. As noted previously, many mtDNA analyses link Polynesians to Taiwan, but Y-chromosome data showed a predominantly 'Melanesian' influence in the Polynesian paternal genepool (Benton *et al*.

Table 1. Models of population expansion to Oceania.

Model	Descriptions
The *Express Train to Polynesia* model by Diamond (1988)	Based on the '*Out of Taiwan*' archaeological hypothesis proposed by Bellwood (1985). According to this hypothesis, common Austronesian ancestors are hill tribe aboriginal people of Taiwan who migrated southwards via the Batanes Islands, Philippines to Remote Oceania without measurable pause in Near Oceania.
The *Slow Boat Model* by Oppenheimer & Richards (2001)	This model suggested Island Southeast Asia as the origin of Polynesians, which is in marked conflict with archaeological chronology.
The *Synthetic Total Evidence Model* (*STEM*) by Chambers (2006)	This model embraces all pattern and process elements including *Out of Taiwan*, gender-biased and reticulated admixture process in Near Oceania and genepool refinement via bottlenecks and founder effects.

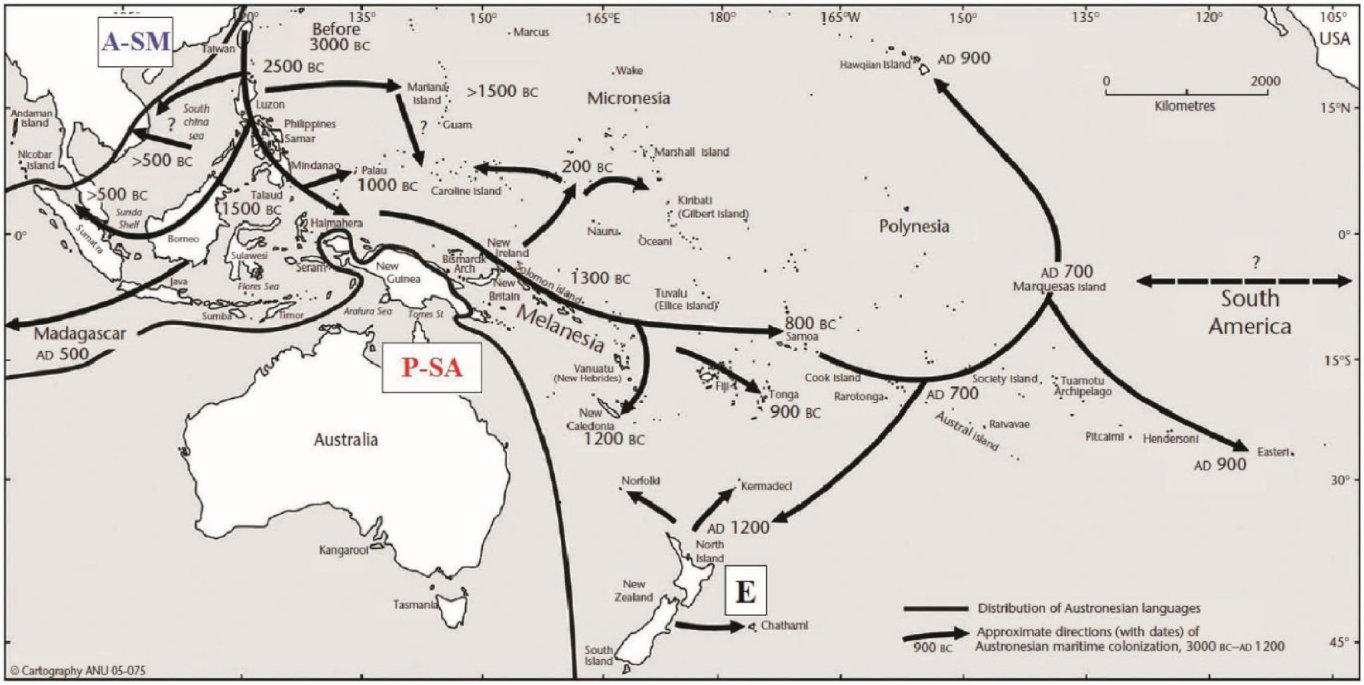

Figure 1. Migration patterns of A-SM in Island South East Asia, Near and Remote Oceania based on archaeological dating. The directions of movements are inferred from sequential chronology and linguistic evidence. Abbreviations: A-SM (Austronesian-speaking Mongoloid), P-SA (Papuan-speaking Australoid) and E (Europeans). This figure is reproduced after Bellwood *et al*. (2011).

2012, Hagelberg *et al*. 1999, Kayser *et al*. 2006, Melton *et al*. 1995, Redd *et al*. 1995, Tabbada *et al*. 2010, Underhill *et al*. 2001). These dual ancestral fractions in present day Polynesian people are associated with matrilocal society practice by ancestral Polynesians which contributed towards sex-biased genetic admixture in Near Oceania before these people later voyaged out to remote Oceania (Cann & Lum 2004, Chambers 2006).

New insights into ancestry in Māori and Polynesians

With this background in mind we can now turn our attention to the ways our recent reports on immune system markers further illustrate this story. Our genetic surveys on human leukocyte antigen (HLA), major histocompatibility complex class I chain-related gene A (MICA), killer cell immunoglobulin-like receptor (KIR), blood group and human platelet antigen (HPA) provide novel ancestry-informative data for Māori and Polynesian people and can be used to test reconstructions of Pacific colonisation history (Askar *et al*. 2013, Edinur *et al*. 2012, 2013a, 2013b, 2013c, Nemat-Gorgani *et al*. 2014, Riccio *et al*. 2013). All these new datasets were compared with those reported for Asia Pacific populations, including their putative ancestors, A-SM and P-SA. Phylogenetic and principal component analyses showed that Polynesian sub-populations are more closely related to one another than either one is to those from other Asia Pacific regions. Estimations made based on HLA-A, -B, -C and -DRB1 allele frequencies show surprisingly wide-ranging A-SM:P-SA ancestral fractions (55:45 to 90:10) in Māori and other Polynesians (e.g. see Figure 2). This phenomenon might appear to reflect different proportions of genetic inputs from their ancestors, but is more likely associated with population histories, which include founder effects and local selective forces.

Overall, our findings are entirely consistent with the expectation that both Polynesians and Māori are intermediate between A-SM and P-SA populations (Kimura *et al*. 2008, Wollstein *et al*. 2010). In particular, Polynesian sub-populations share a common Taiwanese ancestor and have experienced gender-biased admixture with P-SA populations. These results complement previous mtDNA and Y-chromosome haplotype scores frequencies for the VUW DNA Bank samples (Friedlaender *et al*. 2008, Kimura *et al*. 2008, Underhill *et al*. 2001) and thus correspond to the accepted archaeolinguistic reconstruction of Pacific settlement (Bellwood *et al*. 2011, Gray *et al*. 2011, Kirch 2010).

Genetic data collected for Polynesians over the years contribute significant support for key elements of the *Synthetic Total Evidence Model* of Pacific Settlement. This review brings them together for the first time since its first formulation (Chambers 2006) and extends the later accounts (Bellwood *et al*. 2011, Chambers 2013, Chambers & Edinur 2015) which are focussed on support for the Out of Taiwan component. Today, the genepools of Polynesians and Māori are expanding through opportunities for intermarriage with members of other ethnic groups (i.e. principally European). We have demonstrated (e.g. see Figure 3) the significant effects of this admixture in the genepool of present day Māori and Polynesians, and its medical importance is discussed in the following section.

New insights into health in Māori and Polynesians

It is important to recognise New Zealand as a genetically heterogeneous multi-ethnic country, and all medical consequences of this composition have to be explored. We have reported extensively on the unique genetic repertoire in the transfusion and transplantation antigens and genes in Māori and Polynesians as compared with other well characterised populations such as Europeans and North Americans. Currently, there is a general shortage of studies in Māori and Polynesians and their genetic associations, drug responses, and medical conditions, including various autoimmune diseases. These include many such as subcutaneous T cell paniculitis and diabetes, which are common to Polynesians, or like Sydenham's chorea, which is disproportionately common to them (Jackson & Lennon 2015, Woo *et al*. 2003). However, Māori and Polynesians are often unaffected by autoimmune diseases which afflict Europeans,

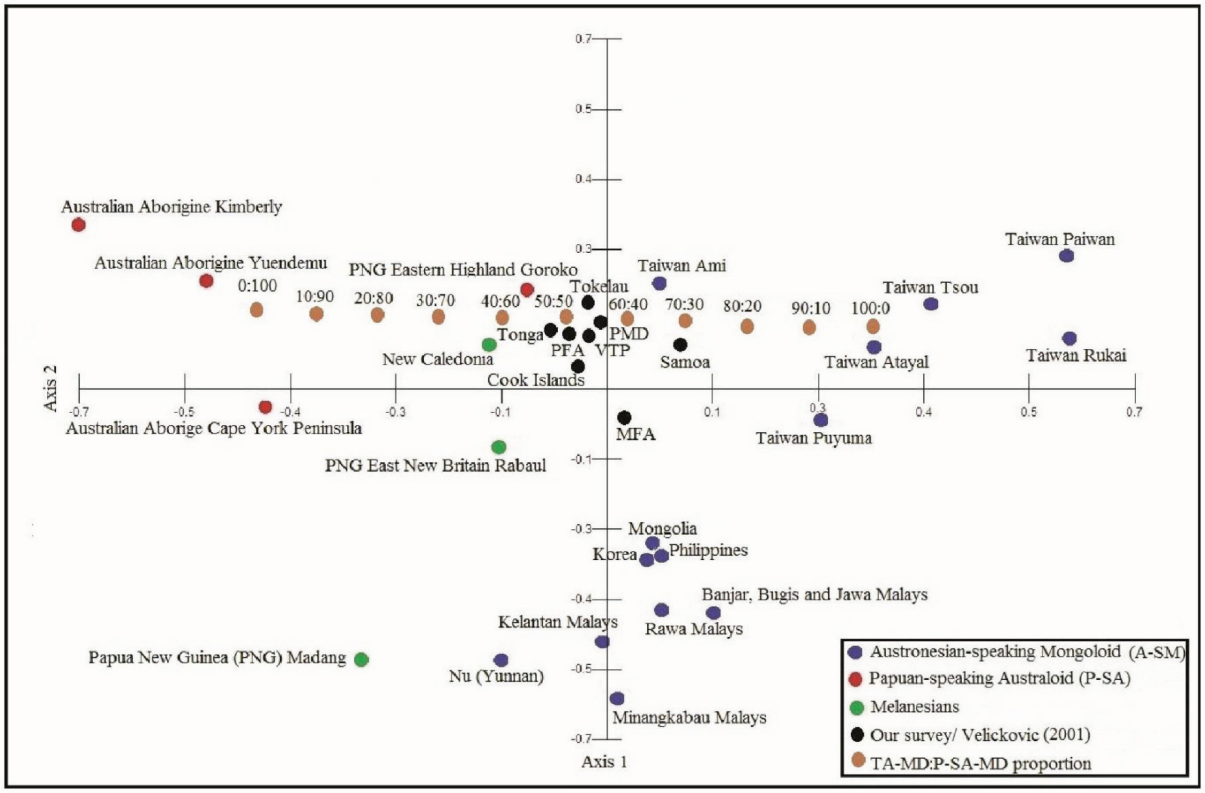

Figure 2. HLA class I and II allele frequencies were used to estimate ancestral fraction in Māori and Polynesian sub-populations based on simulated proportions of Taiwan Aborigines (TA: Taiwan Ami, Atayal, Paiwan, Rukai, Puyuma and Tsou) and Papuan-speaking Australoids (P-SA: Papua New Guinea Goroko and West Schrader Ranges) metadatasets (MD). Reference populations obtained from Edinur *et al*. (2009), Gonzalez-Galarza *et al*. (2011), Lin *et al*. (2000), Main *et al*. (2001), Velickovic (2001), Velickovic *et al*. (2002). Abbreviations: A-SM = Austronesian-speaking Mongoloid, P-SA = Papuan-speaking Australoid, MFA = Māori with Full Ancestry, PFA = Polynesians with Full Ancestry and PNG = Papua New Guinea.

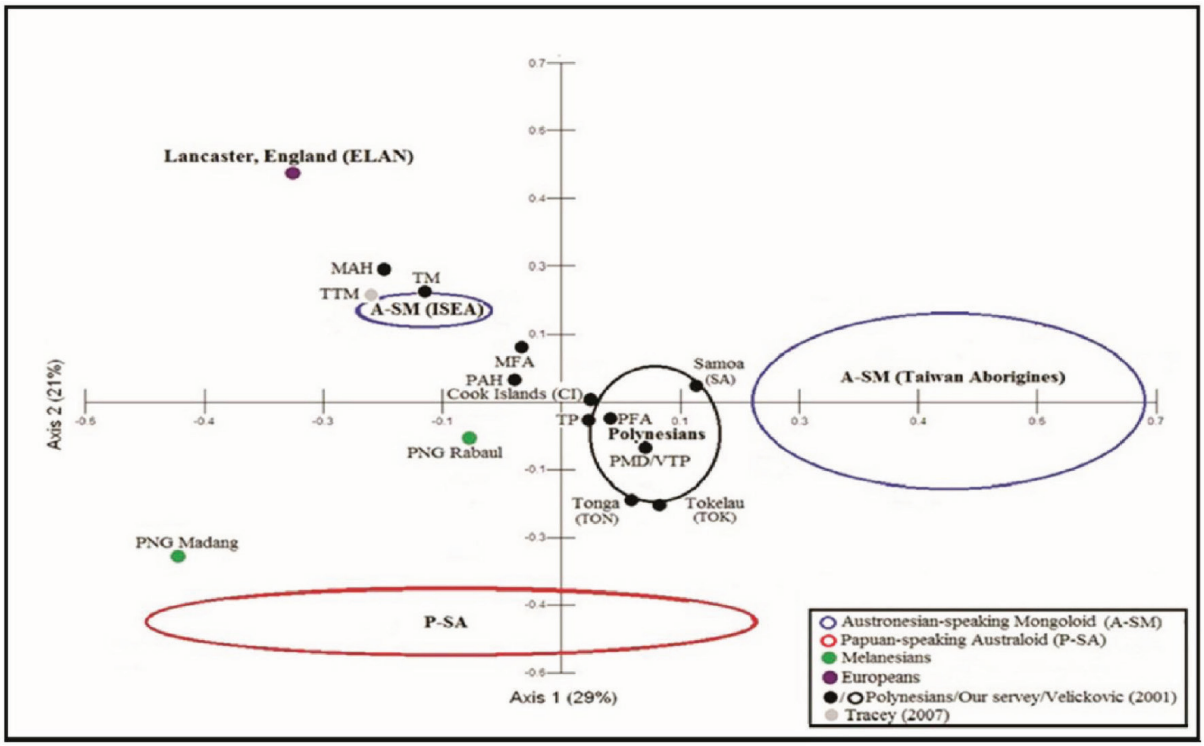

Figure. 3. PCO plot constructed using HLA class I and II allele frequencies shows Polynesians falling as intermediate between cumulative A-SM and P-SA genepools. Māori with full ancestry (MFA) lie close to the general Polynesian cluster, and admixed Māori groups (TM, MAH and TTM) are displaced towards the European reference, ELAN. Reference populations obtained from Edinur *et al*. (2009), Gao *et al*. (1992a, 1992b), Gonzalez-Galarza *et al*. (2011), Hagelberg *et al*. (1999), Lin *et al*. (2000), Mack *et al*. (2000), Main *et al*. (2001), Tracey & Carter (2006), Tracey (2007), Velickovic (2001), Velickovic *et al*. (2002). Abbreviations: TM = Total Māori, MFA = Māori with Full Ancestry, MAH = Māori with Admixed History, TP = Total Polynesians, PFA = Polynesians with Full Ancestry, PAH = Polynesians with Admixed History, VTP = Velickovic Total Polynesians (Cook Islands + Tokelau + Tonga + Samoa), PMD = Polynesians Meta Dataset (VTP + PFA), TTM = Tracey Total Māori, A-SM = Austronesian-speaking Mongoloids, P-SA = Papuan-speaking Australoids.

such as ankylosing spondylitis, uveitis, psoriasis, rheumatoid vasculitis, and coeliac disease. These disorders are all associated with particular types of HLA, MICA and KIR alleles that are common in Europeans. Indeed, the complex issue of admixture fraction and methods for its determination present a serious potential barrier to the wider introduction of genetic-based medicine (Callister *et al*. 2015).

Increasing admixture with Europeans may mean that 'European autoimmune diseases' such as those above may become more common in self-declared Māori and Polynesian patients. We stress that simply pointing out that such differences exist as real phenomena does not in any way imply making value judgements about them or suggest that any one group may be genetically superior to another one. Nor should it be taken to imply fatalism in the sense that one might be doomed by ancestry to develop a particular set of conditions or in the sense that genes alone determine an individual's fate. So these observations should not be interpreted as evidence to reinforce negative stereotypes of Māori, Pacific Islanders or Europeans. All these ideas are examples of outmoded 'Biological Determinism' thinking and ignore the important interactions between genotypes and environments. It is clear that changes in one's environment or behaviour can often be positive influences on disease risk schedules.

Intermarriage between Polynesians and other ethnicities is not uncommon in New Zealand. Our statistical inferences showed a possibility of alloimmunisation during pregnancy (i.e. neonatal alloimmune thrombocytopenia: NAIT) in Europeans and Polynesians and the risk is increased for mixed marriage. These are due to the highly polymorphic nature of loci encoded for blood group and human platelet antigens and the presence of less frequent genotypes (HPA-1bb, HPA-3bb, and HPA-5bb among Europeans and HPA-6bb in PFA) in both population groups (see Bennett *et al*. (2002) and Edinur *et al*. (2013b)) and for HPA genotypes in Europeans and Polynesians. Several cases of HLA antibody-mediated NAIT have been reported, including HLA types (HLA-B*27 and HLA-B*56, respectively) that are common to Europeans and Polynesians (Hutchinson *et al*. 2015, Thude *et al*. 2006). The tissue type HLA-B*56 is already common in Polynesians (gene frequency: 0.03–0.34) and intermarriage with Europeans may increase the frequency of the tissue type HLA-B*27 (present gene frequency: 0.00–0.02) in Polynesians (Whyte *et al*. 2005). All these might lead to an increase in NAIT cases in Polynesians in New Zealand. Thus, prenatal diagnostics and genetic counselling may become the future preventive healthcare for some couples in New Zealand.

Several markers tested in Māori and Polynesians are characteristic of tissue identity and important in determining compatibility in transplantation (ABO, HLA, MICA and KIR) and transfusion (blood groups including ABO, Rhesus and Kell and HPA). Incompatibility between donor and recipient may lead to adverse effects including sensitisation, rejection, graft versus host disease and haemolytic transfusion reaction (Anstee 2009, Wise & Carter 2002). Therefore, knowledge on the prevalence and expression of these markers at the population level will help to design an efficient donor recruitment strategy for blood, stem cells and organ donation and will facilitate donor centres searching for donors with unique profiles. In general, feasibility of finding suitable donors for Polynesian and Māori patients is higher within their own ethnic groups, as they share common and unique genepools. In this context, family donation is most likely to be an efficient way to maintain sufficient blood/organ supply in transfusion and transplantation and is acceptable in the Polynesian extended family culture (Wurtzburg 2003). However, patients with rarer genotypes and haplotypes present a great challenge for recruitment centres in searching for a compatible donor. The highly polymorphic loci encoding the clinically relevant transplantation and transfusion antigens together with past episodes of natural selection and admixture have equally introduced what are rare genotypes in Māori and Polynesians, but which may be common in other populations. One good example is the presence of the tissue type haplotype (e.g. HLA*02:12-C*07:02-B*39:05-DRB1*08:02), which is common in Amerindians but not in Polynesians (Edinur *et al*. 2013a, Lie *et al*. 2007). This haplotype, and only this Amerindian-specific haplotype, has been observed in a number of New Zealand patients and donors tested by the Tissue Typing Laboratory, New Zealand Blood Service (P Dunn, personal communication). The very limited genetic contribution from Amerindians to the Polynesian genepool is associated with the South American slave trade in the 18th century and this factor has also contributed towards a reduced genetic variability in several Polynesian sub-populations (Maude 1981). However, all these datasets confirm that those claiming full Māori ancestry (i.e. = those with four Māori grandparents) do make up a significant fraction of the contemporary population (perhaps as high as 30–50%). Nonetheless, Polynesian and Māori genepools are becoming more diverse, largely due to inter-group marriage with those from the European lineages. As a consequence, the numbers of available donors for un-admixed Polynesian and Māori patients become smaller, but increase the number of potential donor and recipient pairs that belong to the admixed group. This consideration may be critical in some situations. For instance, progeny of first generation admixture are most likely to find donors among similar individuals, because they have an equal mix of Polynesian and European HLA genes. Recruitment of blood and stem cell donors in Māori and Polynesians in New Zealand still needs to increase even further in order to capture enough donors with mixed ethnicity.

Recently, Cornwall *et al*. (2015) conducted a survey to study New Zealanders' knowledge and attitudes to organ and tissue donation. Their findings showed limited knowledge, but positive support among the younger generation of New Zealand. We have also reported on the characteristics of donors recruited by the New Zealand Bone Marrow Donor Registry and demonstrated that an average of 80% of newly recruited donors have a unique HLA (i.e. individual specific) phenotype not found elsewhere. A search of Bone Marrow Donors Worldwide (BMDW; www.BMDW.org), a co-operation of 75 stem cell registries with 25 million donors, shows that Polynesians are under-represented among worldwide donors (Edinur *et al*. 2015). Together these present a great challenge to find compatible donors, especially for Polynesian patients. In this context, the heterogeneous and admixed society of New Zealand requires a combination of more efficient and holistic approaches to recruitment of larger numbers of Polynesian donors, a high-throughput molecular platform for donor- and recipient-matching plus increasing public awareness and knowledge on organ and stem cell donation (Cornwall *et al*. 2015, Edinur *et al*. 2015).

Our research has also been directed to assess the new molecular blood group and HPA typing methods in Polynesian and Māori populations. Scores for other loci are based on the application of the pre-existing and established genotyping technologies (e.g. Luminex v. sequencing for HLA and KIR typing). Diagnostic kits or molecular techniques have been tested for other populations which may or may not cover genetic variants

in Māori and Polynesians. Our validation using three different blood group and HPA genotyping methods (i.e. PCR-SSP, SBT and SNP assay) gave 100% concordance and thus reflects the accuracy of the DNA-based methods. Each molecular platform should detect all known polymorphisms associated with cellular expression, or otherwise they would lead to false prediction of phenotypes. For example, commercial PCR-SSP kits used in our survey do not include Jk_{null} and HPA-6 variants which are common or polymorphic in A-SM populations including Polynesians and Māori. Thus, routine uncritical application of these kits would lead to false predictions and will subsequently increase risk of alloimmunisation. Overall, there is compelling evidence for the wider application of molecular approaches for HLA, KIR, MICA, blood group and HPA typing. Molecular methods show exact variations in particular genes and have been shown to improve resolution of polymorphic loci to a precision that could not previously be achieved using serological approaches (Dunn 2011, 2015, Patnaik *et al*. 2012, Robinson *et al*. 2013). In addition, genotyping is the preferred technique when there are no reliable antisera, poor cell expression and cross reactivity. At present, several molecular methods as simple as PCR-SSP to rapid and high-throughput PCR-SSOP based platforms such as Luminex and SNP genotyping assay have been tested and used by others for HLA, MICA, KIR, blood group and HPA typing, individually (Dunn 2011, 2015, Middleton 2005, Veldhuisen *et al*. 2009, Wu & Csako 2006). Certain clinical cases require matching not only for ABO, but also for HPA and HLA loci (e.g. refractoriness to platelet transfusion and transfusion-related acute lung injury). It is expected that these loci could be genotyped simultaneously in the near future, using a single high-throughput platform. The application of molecular techniques has a promising future in clinical settings and the thrust of our intended message is that serological methods have served well for a prolonged period, but are now seriously challenged by newer DNA-based technologies and a lack of serological reagents. We have tested some of the molecular techniques on Māori and Polynesian DNA samples and examined various aspects of their performance including their economics (Edinur *et al*. 2013c). Overall, we find them to be relatively expensive, but very reliable especially for the genetically heterogeneous population of New Zealand.

Finally, we point to the fact that our new databases are of interpretive, predictive and prospective value. For instance, some studies are presently forced to speculate that their findings are most likely due to admixture between Māori and Europeans. They can now validate their conclusions, by asking subjects the key diagnostic questions about their grandparents by retrospective interview. Our experience reported here also shows that this would now be possible by screening the samples for the ancestry informative HLA markers reported in our studies (Edinur *et al*. 2012, 2013a, 2013b, 2013c, Nemat-Gorgani *et al*. 2014, Riccio *et al*. 2013). The predictive value of our new data is such that as novel potentially autoimmune disorders, such as Sydenham's chorea, are found to have differing incidence between Māori and European, the most likely candidate immune system markers will be those showing greatest differences in allele frequency between the two groups. Further, when new HLA associations are eventually found for diseases, the relative incidence of the disease in the two groups will be predictable in part from the relative occurrence of the associated marker in the two groups. The data are of prospective value to all other populations with Austronesian ancestry (these presently number in excess of 350 million people, living mainly in SE Asia). In complementary fashion, our studies show that data obtained overseas may give valuable pointers to candidate systems and markers of value to New Zealand medicine. We are currently conducting a series of studies with Malaysian subjects (Abd Gani *et al*. 2015, NurWaliyuddin *et al*. 2014, Wan Syafawati *et al*. 2015) which will help to test this proposition further. The genetic screening programme in Malaysia, especially on the predominantly A-SM sub-populations (i.e. Malay subethnic groups), also provides a reference standard for genetic markers (i.e. human neutrophil antigens and cytokines) that have never previously been tested in Māori and Polynesians (Manaf *et al*. 2015, Norhalifah *et al*. 2015).

In our view extended investigation of the KIR system has particular value and urgency. These systems have been implicated in many biological and medical processes (Riccio *et al*. 2013). Māori and Polynesians have an unusual frequency (59–65% - 31 allelic types) of the reduced KIR A haplotype (held to be significant in combating disease) compared with the extended KIR B haplotype (only 35–41% - 18 allelic types and held to be of more significance in reproduction). Their KIR haplotypes are also unusual with respect to the range of HLA Class I signals that they recognise; namely HLA-A > HLA-B and HLA-C. Thus it is clear that the performance of the KIR system may be radically different in Māori and Polynesian patients compared with Europeans. For instance, these differences could include the roles and associations involved in the vital recognition of 'missing self' (i.e. down-regulated cell surface markers) in virus infected cells and tumours. This might, therefore, include an important role in 'graft versus leukaemia' in stem cell therapy (Ruggeri *et al*. 2002). Unfortunately, however, despite enormous research efforts, the clinical relevance of KIR and its interaction with HLA remains elusive.

Conclusion

The central theme of our research programme is the development and application of molecular methods to measure genetic variability in Māori and Polynesian populations. Each experimental work was designed to study ancestry and improve health outcomes, e.g. as presented here for transplantation and transfusion medicine. Our new experimental works on blood groups, HPA, HLA and MICA and most recently on KIR showed differences between Polynesian and European genepools and demonstrated the reliability of current genotyping platforms that would suit well the needs of transfusion and transplantation centres, an important clinical aid in matching organs/stem cells and providing safe blood. These datasets were used for dual analyses of ancestry and health and can also be used as the reference standard for future study of diseases in Māori and Polynesians.

Acknowledgements

Experimental works have been supported by a wide range of agencies; New Zealand Blood Service Tissue Typing Laboratory, New Zealand Bone Marrow Donor Registry office, Leukaemia and Blood Cancer New Zealand, Ministry of Higher Education Malaysia (MOHE E1515) and Victoria University of Wellington. We are very grateful by the support, consideration, advice and suggestions given by Dr Paul Norman (Stanford University), Dr Peter Parham (Stanford University), Dr Zlatibor Velickovic (University of Sydney, Australia), Medhat Askar (Transplant Centre, Cleveland Clinic), Patrick Reville (Transplant Centre, Cleveland Clinic) and Peter Brescia (One Lambda, CA, USA). We acknowledge with thanks technical assistance in preparing the manuscript provided by Manaf Siti Mariam.

References

Abd Gani R., Manaf S.M., Zafarina Z., Panneerchelvam S., Chambers G.K., Norazmi M.N., Edinur H.A. 2015. Molecular blood group typing in Banjar, Jawa, Mandailing and Kelantan Malays in Peninsular Malaysia. *Transfusion and Apheresis Science 53(1)*: 69–73.

Anstee D.J. 2009. Red cell genotyping and the future of pretransfusion testing. *Blood 114(2)*: 248–256.

Askar M., Daghstani J., Thomas D., Leahy N., Dunn P., Claas F., Doran S. *et al*. 2013. 16th IHIW: global distribution of extended HLA haplotypes. *International Journal of Immunogenetics 40(1)*: 31–38.

Bellwood P. 1985. *Prehistory of the Indo-Malay Archipelago*. Sydney: Academic Press.

Bellwood P., Chambers G.K., Ross M., Hung H.C. 2011. Are 'cultures' inherited? Multidisciplinary perspectives on the origins and migrations of Austronesian-speaking peoples prior to 1000 BC. Pp 321–354 in: Roberts B., Linden M. (eds) *Investigating Archaeological Cultures*. Dordrecht: Springer.

Bennett J.A, Palmer L.J., Musk A.W., Erber W. N. 2002. Gene frequencies of human platelet antigens 1–5 in indigenous Australians in Western Australia. *Transfusion Medicine 12(3)*: 199–203.

Benton M., Macartney-Coxson D., Eccles D., Griffiths L., Chambers G., Lea R. 2012. Complete mitochondrial genome sequencing reveals novel haplotypes in a Polynesian population. *PLoS One 7(4)*: e35026.

Callister P., Chambers G.K., Didham R. 2015. 'Marrying' demographic and genetic measures? New tools for understanding New Zealand population subgroups. Working paper 2015:46 online at: http://callister.co.nz/papers.htm

Cann R.L., Lum J. K. 2004. Dispersal ghosts in Oceania. *American Journal of Human Biology 16(4)*: 440–451.

Chambers G.K. 2006. Polynesian genetics and Austronesian prehistory. Pp. 299–319 in: Simanjuntak T., Pojoh I., Hisyam M. (eds) *Austronesian Diaspora and the Ethnogeneses of People in Indonesian Archipelago*. Indonesian Institute of Sciences (LIPI). Jakarta.

Chambers G.K. 2008. Genetics and the origins of the Polynesians. Pp. 489–497 in: Cooper D., Kehrer-Sawatzki H. (eds) *Handbook of human molecular evolution*. John Wiley & Sons Inc. Chichester.

Chambers G.K. 2013. Genetics and the origins of the Polynesians. In *Encyclopedia of Life Sciences*. John Wiley & Sons Inc. Chichester.

Chambers G.K., Edinur H.A. 2013. Genetic relationships between Malays and Māori. Pp. 6–37 in: Rahman W., Higgins T. (eds) *The changing values of Malays, Māori and Pacific Islanders*. Chair of Malay Studies & Victoria University Foundation. New Zealand.

Chambers G.K., Edinur H.A. 2015. The Austronesian Diaspora: A Synthetic Total Evidence Model. *Global Journal of Anthropology Research 2(2)*: 53–65.

Chambers G.K., Marshall S.J, Robinson G.M., Maguire S., Newton-Howes J., Chong N.L. 2002. The genetics of alcoholism in Polynesians: alcohol and aldehyde dehydrogenase genotypes in young men. *Alcoholism: Clinical and Experimental Research 26(7)*: 949–955.

Clark A.G., Hamilton J.F., Chambers G.K. 1995. Inference of population subdivision from the VNTR distributions of New Zealanders. *Genetica 96(1–2)*: 37–49.

Cornwall J., Schafer C., Lal N., D'Costa R., Nada-Raja S. 2015. New Zealand university students' knowledge and attitudes to organ and tissue donation. *New Zealand Medical Journal 128(1418)*: 70–79.

Diamond J.M. 1988. Express train to Polynesia. *Nature 336*: 307–308.

Dunn P.P. 2011. Human leucocyte antigen typing: techniques and technology, a critical appraisal. *International Journal of Immunogenetics 38(6)*: 463–473.

Dunn P.P. 2015. Novel approaches and technologies in molecular HLA typing. *Methods in Molecular Biology 1310*: 213–230.

Edinur H.A., Zafarina Z., Spínola H., Nurhaslindawaty A.R., Panneerchelvam S., Norazmi M. N. 2009. HLA polymorphism in six Malay subethnic groups in Malaysia. *Human Immunology 70(7)*: 518–526.

Edinur H.A., Dunn P.P., Hammond L., Selwyn C., Velickovic Z., Lea R.A., Chambers G.K. 2012. Using HLA loci to inform ancestry and health in Polynesian and Māori populations. *Tissue Antigens 80(6)*: 509–522.

Edinur H.A., Dunn P.P., Hammond L., Selwyn C., Brescia P., Askar M., Reville P., Velickovic Z.M., Lea R.A., Chambers G.K. 2013a. HLA and MICA polymorphism in Polynesians and New Zealand Māori: implications for ancestry and health. *Human Immunology 74(9)*: 1119–1129.

Edinur H.A., Dunn P.P., Lea R.A., Chambers G.K. 2013b. Human platelet antigens frequencies in Māori and Polynesian populations. *Transfusion Medicine 23(5)*: 330–337.

Edinur H.A., Dunn P.P., Lea R.A., Chambers G.K. 2013c. Molecular approaches to transfusion medicine in Polynesians and Māori in New Zealand. *International Journal of Immunogenetics 40(6)*: 460–470.

Edinur H.A., Chambers G.K., Dunn P.P. 2015. Recent developments in transplantation and transfusion medicine. *Annals of Transplantation 20*: 424–429.

Friedlaender J.S., Friedlaender F.R., Reed F.A., Kidd K.K., Kidd J.R., Chambers G.K., Lea R.A. *et al*. 2008. The genetic structure of Pacific Islanders. *PLoS Genetics 4(1)*: e19.

Gao X., Bhatia K., Trent R.J., Serjeantson S.W. 1992a. HLA-DR, DQ nucleotide sequence polymorphisms in five Melanesian populations. *Tissue Antigens 40(1)*: 31–37.

Gao X., Veale A., Serjeantson S.W. 1992b. HLA class II diversity in Australian aborigines: unusual HLA-DRB1 alleles. *Immunogenetics 36(5)*: 333–337.

Gearry R.B., Lea R.A., Roberts R.L., Chambers G.K., Barclay M.L., Kennedy M.A. 2006. CARD15 allele frequency differences in New Zealand Māori: ancestry specific susceptibility to Crohn's disease in New Zealand? *Gut 55(4)*: 580–580.

Ghodke Y., Joshi K., Chopra A., Patwardhan B. 2005. HLA and disease. *European Journal of Epidemiology 20(6)*: 475–488.

Gonzalez-Galarza F.F., Christmas S., Middleton D., Jones A.R. 2011. Allele frequency net: a database and online repository for immune gene frequencies in worldwide populations. *Nucleic Acids Research 39(suppl 1)*: D913–D919.

Gosling A.L., Buckley H.R., Matisoo-Smith E., Merriman T.R. 2015. Pacific populations, metabolic disease and 'Just-So Stories': A critique of the 'Thrifty Genotype' hypothesis in Oceania. *Annals of Human Genetics 79(6)*: 470–480.

Gray R.D., Drummond A.J., Greenhill S.J. 2009. Language phylogenies reveal expansion pulses and pauses in Pacific settlement. *Science 323(5913)*: 479–483.

Gray R.D., Atkinson Q.D., Greenhill S.J. 2011. Language evolution and human history: what a difference a date makes. *Philosophical Transactions of the Royal Society of London B Biological Sciences 366(1567)*: 1090–1100.

Hagelberg E., Kayser M., Nagy M., Roewer L., Zimdahl H., Krawczak M., Lio P., Schiefenhövel W. 1999. Molecular genetic evidence for the human settlement of the Pacific: analysis of mitochondrial DNA, Y chromosome and HLA markers. *Philosophical Transactions of the Royal Society of London B Biological Sciences 354(1379)*: 141–152.

Hamilton J.F., Starling L., Cordiner S.J., Monahan D.L., Buckleton J.S., Chambers G.K., Weir B.S. 1996. New Zealand population data at five VNTR loci: validation as databases for forensic identity testing. *Science and Justice 36(2)*: 109–117.

Hutchinson A.L., Dennington P.M., Holdsworth R., Downe L. 2015. Recurrent HLA-B56 mediated neonatal alloimmune thrombocytopenia with fatal outcomes. *Transfusion and Apheresis Science 52(3)*: 311–313.

Jackson C., Lennon D.: 2015. *Auckland Regional Rheumatic Fever Register*. Auckland: Ministry of Health.

Kayser M., Brauer S., Cordaux R., Casto A., Lao O., Zhivotovsky L.A., Moyse-Faurie C. *et al*. 2006. Melanesian and Asian origins of Polynesians: mtDNA and Y chromosome gradients across the Pacific. *Molecular Biology and Evolution 23(11)*: 2234–2244.

Kimura R., Ohashi J., Matsumura Y., Nakazawa M., Inaoka T., Ohtsuka R., Osawa M., Tokunaga K. 2008. Gene flow and natural selection in oceanic human populations inferred from genome-wide SNP typing. *Molecular Biology and Evolution 25(8)*: 1750–1761.

Kirch P.V. 2010. Peopling of the Pacific: A holistic anthropological perspective. *Annual Review of Anthropology 39*: 131–148.

Lea R., Chambers G. 2007a. Monoamine oxidase, addiction, and the 'warrior' gene hypothesis. *New Zealand Medical Journal 120 (1250)*: U2441.

Lea R., Chambers G. 2007b. Pharmacogenetics in Admixed Populations in Polynesia. Pp. 164–189 in: Suarez-Kurtz G. (ed.) *Pharmacogenomics in admixed populations*. Landes Bioscience. Austin, TX.

Lea R., Benowitz N., Green M., Fowles J., Vishvanath A., Dickson S., Lea M., Woodward A., Chambers G., Phillips D. 2005. Ethnic differences in nicotine metabolic rate among New Zealanders. *New Zealand Medical Journal 118(1227)*: U1773

Lea R.A., Roberts R.L., Green M.R., Kennedy M.A., Chambers G.K. 2008. Allele frequency differences of cytochrome P450 polymorphisms in a sample of New Zealand Māori. *New Zealand Medical Journal 121(1272)*: 33–37.

Lie B.A, Dupuy B.M., Spurkland A., Fernández-Viña M.A., Hagelberg E., Thorsby E. 2007. Molecular genetic studies of natives on Easter Island: evidence of an early European and Amerindian contribution to the Polynesian gene pool. *Tissue Antigens 69(1)*: 10–18.

Lin M., Chu C., Lee H.L., Chang S.L., Ohashi J., Tokunaga K., Akaza T., Juji T. 2000. Heterogeneity of Taiwan's indigenous population: possible relation to prehistoric Mongoloid dispersals. *Tissue Antigens 55(1)*: 1–9.

Lipson M., Loh P.R., Patterson N., Moorjani P., Ko Y.C., Stoneking M., Berger B., Reich D. 2014. Reconstructing Austronesian population history in island Southeast Asia. *Nature Communications 5*: 4689.

Mack S.J., Bugawan T.L., Moonsamy P.V., Erlich J.A., Trachtenberg E.A., Paik Y.K., Begovich A.B. *et al*. 2000. Evolution of Pacific/Asian populations inferred from HLA class II allele frequency distributions. *Tissue Antigens 55(5)*: 383–400.

Main P., Attenborough R.D., Chelvanayagam G., Gao X. 2001. The peopling of New Guinea: evidence from class I human leukocyte antigen. *Human Biology 73(3)*: 365–383.

Manaf S.M., NurWaliyuddin H.Z., Panneerchelvam S., Zafarina Z., Norazmi M.N., Chambers G.K., Edinur H.A 2015. Human neutrophil antigen profiles in Banjar, Bugis, Champa, Jawa and Kelantan Malays in Peninsular Malaysia. *Blood Transfusion 13(4)*: 510–515.

Matisoo-Smith E. 2015. Ancient DNA and the human settlement of the Pacific: A review. *Journal of Human Evolution 79*: 93–104.

Maude H.E.: 1981. Pp. 1862–1864 in: *Slavers in Paradise: the Peruvian slave trade in Polynesia.* Stanford University Press.

Melton T., Peterson R., Redd A.J., Saha N., Sofro A.S., Martinson J., Stoneking M. 1995. Polynesian genetic affinities with Southeast Asian populations as identified by mtDNA analysis. *American Journal of Human Genetics 57(2)*: 403–414.

Middleton D. 2005. HLA typing from serology to sequencing era. *Iranian Journal of Allergy, Asthma and Immunology 4(2)*: 53–66.

Mourant A.E., Kopec A.C., Domaniewska-Sobczak K.: 1978. *Blood Groups and Diseases. A study of associations of diseases with blood groups and other polymorphisms*: Oxford University Press, London.

Myles S., Lea R.A., Ohashi J., Chambers G.K., Weiss J.G., Hardouin E., Engelken J. *et al*. 2011. Testing the thrifty gene hypothesis: the Gly482Ser variant in PPARGC1A is associated with BMI in Tongans. *BMC Medical Genetics 12*: 10.

Nemat-Gorgani N., Edinur H.A., Hollenbach J.A., Traherne J.A., Dunn P.P., Chambers G.K., Parham P., Norman P.J. 2014. KIR diversity in Māori and Polynesians: populations in which HLA-B is not a significant KIR ligand. *Immunogenetics 66(11)*: 597–611.

Norhalifah H.K., Zafarina Z., Sundararajulu P., Norazmi M.N. and Edinur H.A. 2015. Distribution of cytokine gene polymorphisms in five Malay subethnic groups in Peninsular Malaysia. *International Journal of Immunogenetics 42(3)*: 200–203.

NurWaliyuddin H.Z., Edinur H.A., Norazmi M.N., Sundararajulu P., Chambers G.K., Zafarina Z. 2014. Killer immunoglobulin-like receptor diversity in Malay subethnic groups of Peninsular Malaysia. *International Journal of Immunogenetics 41(6)*: 472–479.

Oppenheimer S., Richards M. 2001. Fast trains, slow boats, and the ancestry of the Polynesian islanders. *Science Progress 84(3)*: 157–181.

Patnaik S.K., Helmberg W., Blumenfeld O.O. 2012. BGMUT: NCBI dbRBC database of allelic variations of genes encoding antigens of blood group systems. *Nucleic Acids Research 40(D1)*: D1023–D1029.

Qidwai T., Khan F. 2011. Tumour necrosis factor gene polymorphism and disease prevalence. *Scandinavian Journal of Immunology 74(6)*: 522–547.

Redd A.J., Takezaki N., Sherry S.T., McGarvey S.T., Sofro A.S., Stoneking M. 1995. Evolutionary history of the COII/tRNALys intergenic 9 base pair deletion in human mitochondrial DNAs from the Pacific. *Molecular Biology and Evolution 12(4)*: 604–615.

Riccio M.E., Buhler S., Nunes J.M., Vangenot C., Cuenod M., Currat M., Di D. *et al*. 2013. 16th IHIW: analysis of HLA population data, with updated results for 1996 to 2012 workshop data (AHPD project report). *International Journal of Immunogenetics 40(1)*: 21–30.

Robinson J., Halliwell J.A., McWilliam H., Lopez R., Parham P., Marsh S.G. 2013. The IMGT/HLA database. *Nucleic Acids Research 41(D1)*: D1222–D1227.

Ruggeri L., Capanni M., Urbani E., Perruccio K., Shlomchik W.D., Tosti A., Posati S. *et al*. 2002. Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants. *Science 295(5562)*: 2097–2100.

Stephens H.A. 2001. MICA and MICB genes: can the enigma of their polymorphism be resolved? *Trends in Immunology 22(7)*: 378–385.

Tabbada K.A., Trejaut J., Loo J.H., Chen Y.M., Lin M., Mirazón-Lahr M., Kivisild T., De Ungria M.C. 2010. Philippine mitochondrial DNA diversity: a populated viaduct between Taiwan and Indonesia? *Molecular Biology and Evolution 27(1)*: 21–31.

Thude H., Schorner U., Helfricht C., Loth M., Maak B., Barz D. 2006. Neonatal alloimmune thrombocytopenia caused by human leucocyte antigen-B27 antibody. *Transfus Medicine 16(2)*: 143–149.

Tracey M. 2007. HLA Allelic Variation in New Zealand Māori. PhD Thesis. University of Otago, Dunedin, New Zealand.

Tracey M.C., Carter J.M. 2006. Class II HLA allele polymorphism: DRB1, DQB1 and DPB1 alleles and haplotypes in the New Zealand Maori population. *Tissue Antigens 68(4)*: 297–302.

Underhill P.A., Passarino G., Lin A.A., Marzuki S., Oefner P.J., Cavalli-Sforza L.L., Chambers G.K. 2001. Māori origins, Y-chromosome haplotypes and implications for human history in the Pacific. *Human Mutation 17(4)*: 271–280.

Veldhuisen B., van der Schoot C.E., de Haas M. 2009. Blood group genotyping: from patient to high-throughput donor screening. *Vox Sanguinis 97(3)*: 198–206.

Velickovic Z. 2001. HLA Polymorphism in Pacific Islands Populations. PhD Thesis. University of Otago, Dunedin, New Zealand.

Velickovic Z.M., Delahunt B., Carter J.M. 2002. HLA-DRB1 and HLA-DQB1 polymorphisms in Pacific Islands populations. *Tissue Antigens 59(5)*: 397–406.

Wan Syafawati W.U., Norhalifah H.K., Zefarina Z., Zafarina Z., Panneerchelvam S., Norazmi M.N., Chambers G.K., Edinur H.A. 2015. Allele frequencies of human platelet antigens in Banjar, Bugis, Champa, Jawa and Kelantan Malays in Peninsular Malaysia. *Transfus Medicine* 25(5): 326–332.

Whyte A.L., Marshall S.J., Chambers G.K. 2005. Human evolution in Polynesia. *Human Biology 77(2)*: 157–177.

Wise D.J., Carter G.R.: 2002. *Immunology: A comprehensive review*: John Wiley & Sons Inc. Chichester.

Wollstein A., Lao O., Becker C., Brauer S., Trent R.J., Nürnberg P., Stoneking M., Kayser M. 2010. Demographic history of Oceania inferred from genome-wide data. *Current Biology 20(22)*: 1983-1992.

Woo C.L.F., Liu K.T., Young B.M.Y. 2003. Case Report: Acute rheumatic fever presenting with Sydenham's chorea. *Hong Kong Journal of Paediatrics (New Series) 8(3)*: 198–202.

Wu Y.Y., Csako G. 2006. Rapid and/or high-throughput genotyping for human red blood cell, platelet and leukocyte antigens, and forensic applications. *Clinica Chimica Acta 363(1)*: 165–176.

Wurtzburg S. 2003. Domestic violence and Polynesian families: Providing appropriate interventions. Pp. 179–196 in: McMaster K., Wells A. (eds) *Innovative Approaches to Stopping Family Violence*. Steele Roberts Ltd, Wellington.

Zhang H., Mooney C.J., Reilly M.P. 2012. ABO blood groups and cardiovascular diseases. *International Journal of Vascular Medicine* 2012: 641917.