

Genetic ancestry and health

Abstract

Information about genetic ancestry has a great value in health studies and other related areas of expertise such as anthropology, forensics and pharmacogenomics. In this review, we highlight several aspects of health that can be significantly improved by better understanding of genetic ancestry. These observations were made possible based on our own medical genetic research in Asia/Pacific populations (i.e. in particular regarding Maori and Orang Asli of New Zealand and Peninsular Malaysia, respectively). The major objectives of this programme of investigations has been to capture and understand genetic diversity in these populations and subsequently to make recommendations in order to maximise the health benefits of this type of population genetic research.

Keywords: genetics, ancestry, health, Polynesians, maori, Malays, orang asli, new Zealand, Malaysia

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Abbreviations: HPA, human platelet antigen; HNA, human neutrophil antigen; MICA, major histocompatibility complex class I chain-related gene A; HLA, human leukocyte antigen; KIR, killer cell immunoglobulin-like receptor; SNP, single nucleotide polymorphism

Introduction

Genetic methods play a significant role in many research areas including medicine, forensics and ancestry study. In this respect, we highlight the ways in which knowledge about genetic ancestry has become an important element in health and medical treatments. This viewpoint is largely based on our own experience working on various genetic markers in Asia/Pacific populations such as Maori, Polynesians, Malays and Orang Asli in New Zealand, Pacific Islands and Malaysia. These diagnostic markers include many loci (e.g. HLA, blood group, HPA, cytokines and HNA) that determine transfusion and transplant success, our immune responses to disease and as causal agents in autoimmunity.

Ancestry and health

We have completed and reported a comprehensive set of ancestrally informative genetic data across many Asia/Pacific populations. These systems include HLA, MICA, KIR, blood group, cytokine, HNA and HPA.¹⁻²⁰ These new datasets not only provide special insights into the ancestry of these people, but also is of significant value in health; as recently reviewed by.²¹⁻²² This is because these genes are determinants of transfusion and transplant success or have been directly associated with other immune and important biological functions. For example, matching of HLA markers between patient and donor is important before proceeding with transplant operations. Certain HLA types have also been shown to be contributing factors in the pathogenesis of various diseases.²³ In the following sub-sections, we will discuss several aspects of health which can be significantly improved based on our understanding of ancestry and genetic diversity in Maori, Malays, Orang Asli and several Polynesian sub-populations.

Allelic variations and disease prevalence: Many diseases have been mapped to particular regions of the human genome and certain allelic types have been associated with high risk of disease susceptibility. In this context, relative risk of autoimmune diseases can be predicted from the prevalence of particular antigen types in a population. For example, medical conditions such as ankylosing spondylitis and rheumatoid arthritis are rare in Maori/Polynesians, but relatively

common among Europeans. They are typically associated with the *HLA-B*27:05* and *HLA-DRB1*04:01* tissue types in Europeans and *HLA-B*27:04* and *HLA-DRB1*04:05* in Asians/Polynesians, respectively.²⁴⁻²⁶ The *HLA-B*27:04* and *HLA-DRB1*04:05* alleles are quite rare in Polynesians (0-0.01 and 0.02-0.08, respectively) which may explain the unusually low occurrence of ankylosing spondylitis and rheumatoid arthritis in Maori/Polynesians.⁵

Candidate genes for disease study: Many genetic markers characterized in various populations across the globe are now available as population datasets and can be readily retrievable from public databases; e.g. see⁸ for Allele Frequencies.net and²⁷ for IPD – Immuno Polymorphism Database. These datasets can be used not only as a reference standard for disease association studies (see later), but also provide important resources to search for candidate susceptibility genes in disease studies. A good candidate gene(s) will be one with greatest differences in allele frequency among populations, including between ethnically related populations which show different schedules of disease prevalence. This is one of the main molecular signatures of the highly polymorphic immune system genes, where patterns of allelic variation at population level are shaped by local demographic or selective factors; e.g. see.^{17,28}

Donor recruitment: In general, compatible donor for a particular patient might best be recruited from his/her own group or other ethnically related groups because they tend to share a common (if not identical) alleles. But this will not always be the case because founder effects, admixture and assimilation over a period of time might change the ancestral fractions in descendant populations. However, this is not the situation for patient with a rare genotype. Instead, their particular genotypic combination in might be more common in another unrelated population; e.g. HNA-5a/5a was reported to be fixed in Orang Kanaq, a Proto-Malay population in Peninsular Malaysia. However, other HNA-5 genotypes (HNA-5a/5b and HNA-5b/5b) are likely also to be present in Orang Kanaq patients, albeit at very low frequency, and their compatible donor would then be most easily found by searching among members of other Orang Asli groups or Malays.⁹⁻¹⁰

The number or size of recruited donor pools should depend on the distributions of allelic spectra at the population level (i.e. particularly those coding for transplant or transfusion determinants such as HLA or the ABO and Rhesus blood groups, respectively). Thus a small and highly homogeneous population might only need to have a small number of recruited donors, while a larger multi-ethnic country with

people having diverse genetic backgrounds (like Malaysia or New Zealand) should have much larger numbers of recruited donors in order to increase the proportions of those with rare phenotype profiles. Special consideration should be given to inter-group marriage which will introduce donors/patients with admixed genetic repertoires. The admixed ethnicity group will have a reduced number of potential donors available from un-admixed groups. However, with the passage of time they will be expected to gradually become the genetically dominant donor group in the population.

Tissue typing strategies: Our various surveys have tested many different molecular techniques for genotyping particular genetic loci; see.^{5,7,20} Our experimental design proved to have value in medical genetic applications. The human genome has now been fully sequenced and very many new molecular typing techniques have been developed, tested and validated for regions of particular interest on chromosomes. Unlike next generation sequencing technology which is fully capable of capturing data from entire coding/non-coding regions, earlier techniques such as sequence based typing (SBT) and sequence specific primer (SSP) recorded only relatively small specifically targeted segments of the human genome. Both, SBT and SSP can reflect serological expression provided that all genetic variants associated with a particular phenotype can be included in the screen. For example, Duffy blood group phenotypes might be falsely identified if clinical analysts only identify the 125G>A SNP (*FY*A* to *FY*B* alleles, respectively) on chromosome 1.²⁹ Two further SNPs (67T>C and 286C>T) in the sequence encoding the *FY*B* allele should also be scored for erythroid silent *Fy(a-b-)* and weak (*Fyabweak*) expression of Duffy antigens, respectively.^{30–32} The erythroid silent variant is common in Africa, but relatively rare in the other populations.^{1,6,33} Hence, high resolution molecular screening of the erythroid silent variant in donors and patients could significantly reduce false prediction rates for Duffy phenotypes in African populations.

Wider applications of population data for ethnically related populations: From a genetic standpoint, any research conducted on individual groups of people might have beneficial values for others, especially for closely related populations. For example, cytokines and HNA have never been genetically characterized in Maori and Polynesians. However, markers frequencies have been reported for both types of loci in some of their Austronesian relatives; namely the Malay subethnic groups.^{9–13} In this context, these datasets from Malay subethnic groups can be used as a prospective guide to values for Maori and Polynesians. Nonetheless, any such inferences should be made with caution because each population might have experienced different evolutionary pressures after they split from one another around 5000 years ago. A most obvious example is that provided by our recent work on cytokine gene SNPs in Malays and Orang Asli where significant differences were recorded not only between Orang Asli groups (Semang vs. Senoi. vs. Proto-Malays), but also between their sub-groups; Lanoh vs. Kensiu vs. Bateq of Semang group.^{12–13}

Conclusion

Overall, our understanding of genetic ancestry has a great potential to inform health and other related areas such as in forensic DNA studies and pharmacogenomics.^{22,34–37} The major challenges ahead are to investigate, describe and understand genetic variability in order to maximise the health benefits of population genetic research.

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Conflicts of interest

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