Arthritis New Zealand Summer Scholarships Reporting Template

Please note that all successful applicants must complete this new reporting template for their Arthritis New Zealand Summer Scholarships project within one calendar month of finishing their study. ***Reports must be no longer than three pages in total.*** *Please also use Calibri (body) font size 11 or 12.*

Name of Student

Daniel Gray

Primary Supervisor's Name

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Primary Supervisor's Institution (including address)

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Project Title

Association between gout status and genetic variants within immune system genes in Māori and Pasifika people.

Statement Regarding Arthritis New Zealand Sponsorship

We would like to thank Arthritis New Zealand for sponsoring this project. Receiving this sponsorship meant this project was able to be conducted in a timely manner. The project was exploratory in nature, and from the results we now have a better idea of the potential usefulness of the data used and several possible genome areas to investigate more closely.

I (Daniel) am very thankful to have received an Arthritis New Zealand summer scholarship. It has provided me with a greater understanding of research as a whole and solidified a number of questions I had previously regarding my career.

Student's Personal Comment About Study/Experience (maximum 250 words)

The ability to work on a summer project has provided me with tremendous insight into the research process. The opportunity to work with a Polynesian dataset in a disease which is close to my own heart, through family connections, has been very fulfilling. Additionally, I have appreciated the opportunity to put into practice the technical skills I learned throughout my undergraduate degree. My investment in the project has reinforced for me why I chose to study science and helped me finalise my decision to pursue a BSc(Hons) in 2022, and beyond that a PhD.

Additionally, this project enabled me to improve my skills in bioinformatics, and data handling. This has been critical to improving my understanding of the topic as it provided experience with what to do when your results are new, the data is imperfect, and everything must be viewed sceptically. A real study like this one differs drastically from the classroom experience and has been an invaluable learning opportunity for me.

Summary of the Project (maximum 500 words)

Please ensure this section is written in accessible language for a non-academic audience and includes: a) the aims of the project; b) key results; c) major point of discussion, and d) conclusion/key recommendations.

Aim and Methodology

This project aimed to investigate whether Polynesian (Māori and Pasifika) specific genetic variants located within inflammatory genes are associated with gout diagnosis.

Whole genome sequencing of 2,119 individuals was used to identify variants across 37 inflammatory genes that had a frequency >1% in at least one Polynesian population, while not being present in non-Polynesian reference data.[1,2] The variants were tested for association with gout in island nation groups consisting of East Polynesian (New Zealand Māori, Cook Island Māori), West Polynesian (Samoan, Tongan, Niuean, Pukapukan), and Other Polynesian ancestries. Variants significantly associated with gout were investigated further ($-\log_{10}(P)$ >4.14 was considered a statistically significant association for a variant pool of this size).

Results

Filtering identified 975 variants across 30 genes for investigation. Seven genes had no variants that fit the allele frequency criteria. Among the identified variants four were non-synonymous, meaning they directly change the protein structure. None of the non-synonymous coding variants were significantly associated with gout. Conversely, synonymous coding variants in *MAPK8* and *CARD8* with nominal associations ($-\log_{10}(P)$ >1.3) were identified. Finally, many of the genes examined showed intronic (non-coding) variants significantly associated with gout (Figure).

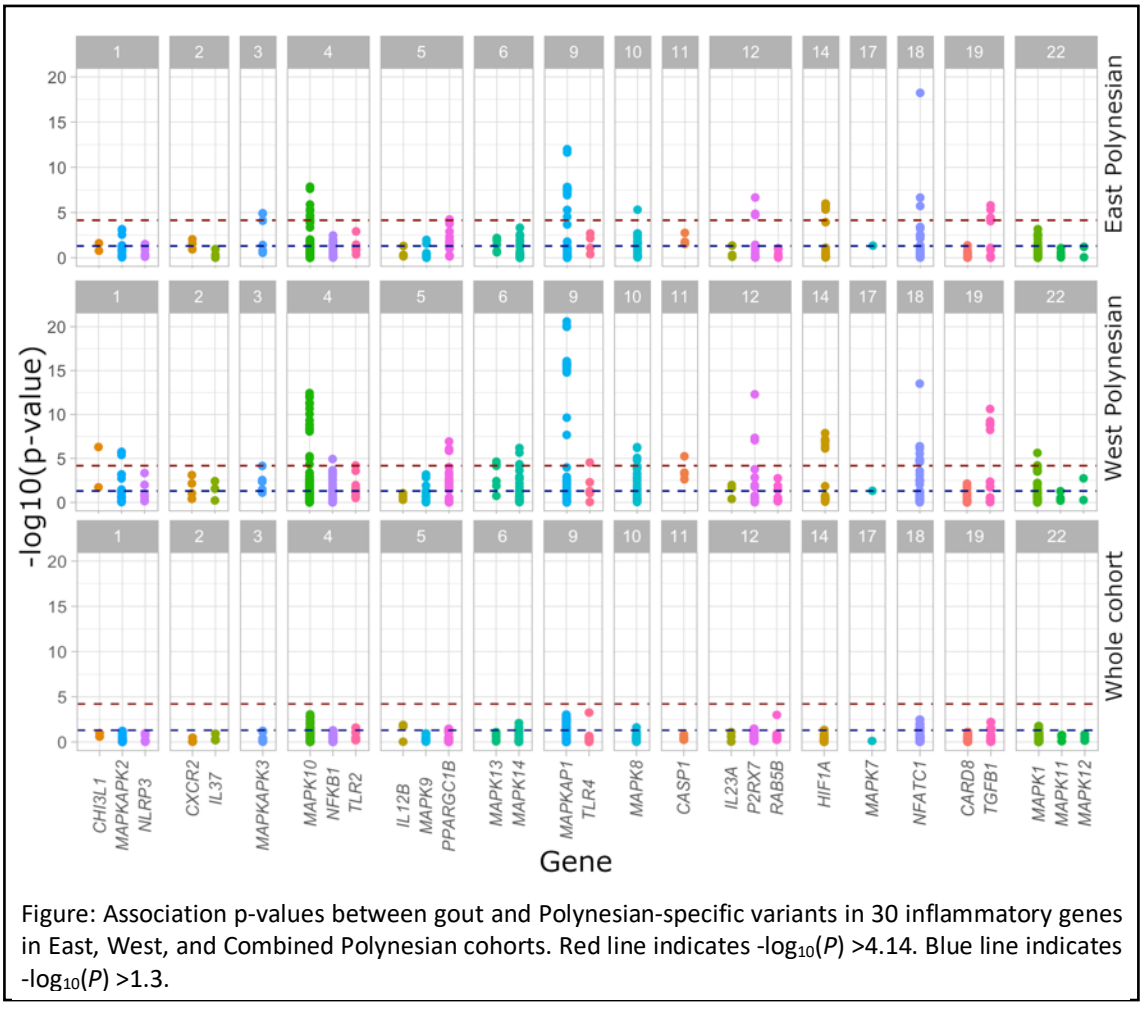

Figure: Association p-values between gout and Polynesian-specific variants in 30 inflammatory genes in East, West, and Combined Polynesian cohorts. Red line indicates $-\log_{10}(P)$ >4.14. Blue line indicates $-\log_{10}(P)$ >1.3.

Discussion

Despite not directly changing proteins, synonymous and intronic variants can effect gene expression levels and regulation.[3] A large number of intronic *MAPKAP1* variants, spanning the entire gene, had a significant association with gout. These *MAPKAP1* variants were in high linkage disequilibrium with each other (meaning they are often inherited together) within all populations studied, providing a novel result for investigation. Interestingly, the protein encoded by *MAPKAP1* functions as a scaffold protein in the interferon pathway,[4] which can regulate inflammasome activation responsible for the symptoms of gout.[5] Crucially, we saw the strongest associations across all our genes when examining a variant within a sub-population and significantly diluted associations in the whole cohort tests. This indicates there may be island nation specific variants or effects and generalising results across all Polynesian populations may not always be appropriate. The associations found in this study add to the mounting evidence that population specific variants are likely contributing to the incidence of gout in Māori and Pasifika communities.[6-9]

Conclusion

Investigation of gout associated Polynesian-specific variants in inflammatory genes may help explain why gout is more common in Māori and Pasifika communities than other Aotearoa New Zealand communities.[10] We know these communities have higher average urate levels,[11] but this does not fully explain the greater prevalence of gout in Polynesian populations as only some individuals with high urate levels and crystal deposition mount the symptomatic immune response characteristic of gout.[12,13] Population-specific studies like this one are important to understanding disease risk in under-studied groups, and may improve our ability to predict gout and introduce early interventions to prevent the disease in at risk individuals. Critically however, all association studies require validation, and statistically significant results do not necessarily mean associations are biologically relevant. As such, further research focusing on validation of the associations found here and the potential importance of the Polynesian-specific linkage disequilibrium block spanning the *MAPKAP1* gene is required.

References (maximum 500 words)

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