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Genetic Basis for Elevated Rheumatic Heart Disease Susceptibility

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ABSTRACT

Rheumatic heart disease is an inflammatory heart disease that affects millions of people around the world. Especially high rates of the disease can be found in Oceania, including the island nation of Samoa. Genetic studies of immune response genes have provided insight into a possible genetic link to increased susceptibility to rheumatic heart disease, including the genes that code for the toll-like receptor (TLR) protein family. One of the functions of TLR proteins is to recognize the presence of bacteria via identification of bacterial flagella.

INTRODUCTION

Searching for a genetic connection to rheumatic heart disease is of interest due to the role genes play in the immune system as they provide the genetic information needed to produce proteins essential for an effective immune response (Figure 1). We have identified families in Samoa with multiple affected individuals and patterns of inheritance that are indicative of elevated genetic risk for disease. We have conducted exome sequencing, variant analysis and segregation analysis to search for the variant(s) that are responsible for this elevated risk.

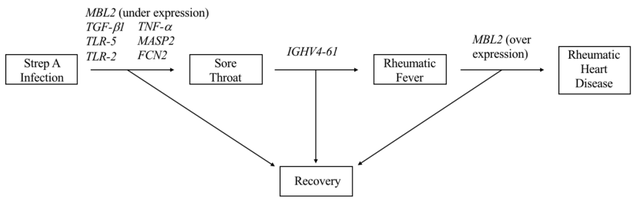

Figure 1: Candidate Genes for Increased Rheumatic Heart Disease Susceptibility. As a Strep A infection progresses towards rheumatic heart disease, genes produce proteins to intervene at difference time points. Polymorphisms in several genes involved in this process have been associated with increased risk of rheumatic heart disease. Depicted are these candidate genes in the relative time position they are employed during an immune response.

METHODS

For pedigree identification we contacted the parents of individuals who screened positive and interviewed them to assess the number and relatedness of other known RHD cases. When multiple affected individuals were identified we obtained consent, conducted a full RHD screening and collected DNA via saliva samples from all available family members. Exome sequence was obtained using IonTorrent technology and analyzed using the Ingenuity Variant Analysis platform (Figure 3).

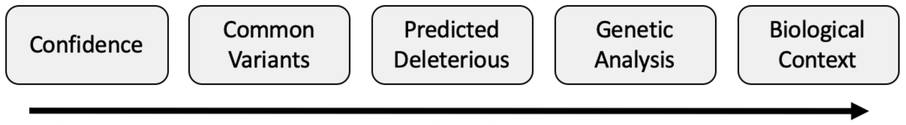

Figure 2: Ingenuity analysis platform workflow used to identify RS5744168 in the TLR5 gene

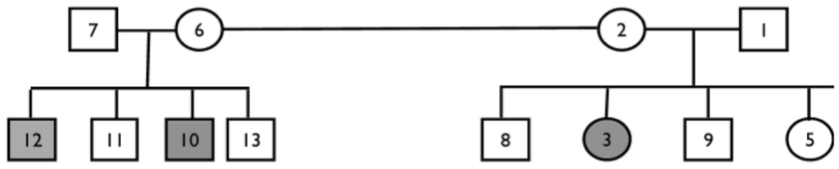

Figure 3: Assuming the mothers have the disease 5 out of 7 have the disease and 0 out of 5 non carriers of a loss of functional variant. 71% have the disease p=0.1280. The p value changes because of the population. We expect that the p value will decrease if the population increases. And if it increases then that's not the SNP that is related to the disease.

RESULTS

We characterized one family with multiple affected individuals. Thirteen individuals were available for screening and DNA collection. Four of the nine offspring, ranging in age from seven years to twenty-seven years, screened positive for RHD. Exome sequence data for these samples has been collected and analyzed. Evidence of RHD was found in 5 of 7 carriers and 0 of 5 non-carriers of a loss of function variant (RS5744168) in Toll-like receptor 5 gene (*TLR5). TLR5* plays an important role in the identification of bacterial flagella for immune response, making it an interesting candidate gene for RHD. Furthermore from the years 2014 the Rheumatic Rescue team screened thousands of children ages 5-15 for rheumatic heart disease in Samoa. DNA samples were collected and analyzed from 114 children diagnosed with rheumatic heart disease with results of analyses (figure 5) The results show that 8 are homozygous and 24 are heterozygous for the mutant allele. With a prevalence of .281 in the sample population.

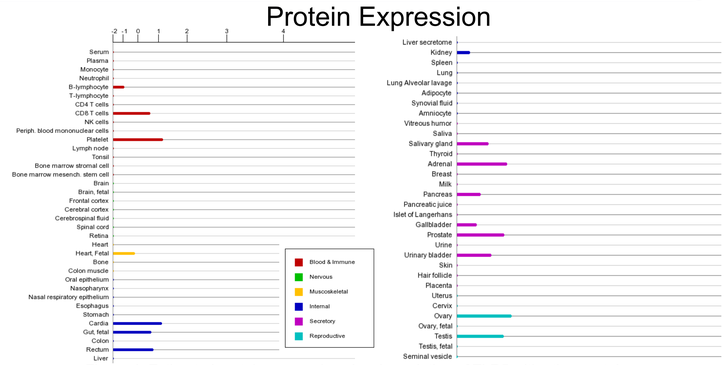

Figure 4: Estimated protein expression showing relation of TLR5 with other proteins

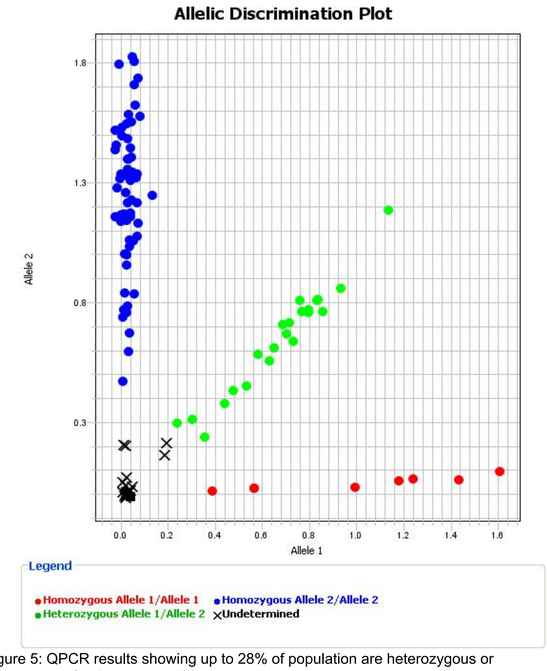

Figure 5: QPCR results showing up to 28% of population are heterozygous or homozygous for the mutant allele

CONCLUSION

The prevalence of RHD in Samoa is known to be elevated. Using a large pedigree we have identified a genetic variant in *TLR5* that may influence susceptibility to RHD. We found significant increases in the mutant allele in our sample population. The global minor allele frequency of the variant rs5744168 is 0.0503 while our observed frequency is 0.281 With this research we can help understand the connection of this variant and the disease and help alleviate suffering of those afflicted with the disease.