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Project: Genetic and epidemiological assessment of BRCA mutation carriers from the New Zealand Familial Breast Cancer Study

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Introduction:
Breast cancer is the most common cancer affecting New Zealand women with around 3000 women being diagnosed each year. Breast cancer affects one in eight New Zealand women with familial or inherited breast cancer accounting for five to ten per cent of all breast cancers. Approximately one third of familial breast cancers result from an inherited mutation in the BRCA1 or BRCA2 genes. These tumour suppressor genes act to control cell cycle and regulate growth when not mutated. When mutated their function is impaired and leaves the carrier with a risk of developing a mutation in the other copy of the gene, leading to unregulated cell growth and breast cancer. The mutations are inherited in an autosomal dominant pattern but they have incomplete penetrance, therefore not all who have the mutation will develop breast or ovarian cancer. The lifetime risk for a BRCA1 mutation carrier can be as much as 80% for breast cancer and up to 50% for ovarian cancers. The New Zealand Familial Breast Cancer Study (NZFBCS) aims to determine what genetic factors in New Zealand women are associated with individual breast cancer risks. The Participants in the NZFBCS are women from high-risk families who may or may not have had breast cancer previously. Presently there are 101 participants in NZFBCS for whom data has previously been collected. This data consists of family, medical and reproductive histories, as well as basic statistics such as weight and height at various point in their lives.

Aim:
To profile genetic, epidemiological and clinical data associated with participants in the NZFBCS.

Method:
All the data from the NZFBCS was converted from paper to electronic format by input into an excel spread sheet. Pathogenicity data on the specific recorded mutations was added and confirmed by a literature search. Using R statistical software summary statistics were developed and compared to national averages and associations between different data points were performed on the cohort. Specific substitution mutations were analysed by cBIO mutation mapper to get mutation positions along the active protein. Only single point substitutions in exons could be analysed by this, other mutations were not analysed. All substitution variants were analysed by Human splice finder, circus and SPANR and compared to previous literature to confirm or refute these claims.

Results:
We found that the study consisted of 83% European participants and 6% Māori participants. New Zealand wide only 69% of the population is European and 12% Maori. Seventy two percent of the participants came from Auckland, Canterbury and Otago with 60% coming from Canterbury and Otago alone. Forty five percent of the cohort has been diagnosed with breast

cancer and 51% had a breast removed. There is specific genetic data on 40% of the cohort. Substitution variants were analysed by the SPANR tool to see if they caused splicing differences that could be a cause of pathogenicity(disease causing). Results were obtained from 13 variants, with 4 showing probable splice variants that were known to be pathogenic, thus it is possible that this predicted splice variation contributes to pathogenicity. When we looked at a string of different epidemiological variables in relation to age diagnosed with breast cancer we found that most of our data points had little to no interaction. Age at birth of first child showed a very slight negative association (P=. Other features, such as height, onset of menstruation, and body mass index (at time of interview and from 18-21 years of age) showed no association with age of cancer onset. The average body mass index of study participants across different age was similar (within the 95% confidence) to the New Zealand average published by the NZ Health Survey

The study is still relatively small with only 101 participants at the time of this evaluation. Some of the results could be due to an overrepresentation of Europeans and an underrepresentation of Māori, Asian and Pacific Island Peoples. The low number of regional councils representing the bulk of the participants could explain this ethnic skew. As the study grows the number of participants from underrepresented councils such as Gisborne, Hawkes Bay and Taranaki will grow and the ethnic proportions should begin to better represent New Zealand as a whole. The reason that the percentage of the cohort having at least one breast removed is greater than those who have had breast cancer is likely because these women are at high risk of developing breast cancer. Thus, many have undergone prophylactic breast removal to decrease their risk of getting breast cancer. All the associations were supported by the previous literature as there is lots of literature on these variables and their influence on Breast cancer but no correlation has yet been found in BRCA cohorts. Any potential splice sites would need to undergo protein and RNA analyses to determine if the mutation actually affected splicing and therefore protein structure and could contribute to pathogenicity.

Conclusion:

This study is at present small and therefore has a few issues that will likely be fixed as the study grows and expands to encompass a greater diversity and therefore more accurate picture of BRCA mutation carriers in NZ. This would allow the study to contribute more thoroughly to ENIGMA and CIMBA and hopefully contribute to reducing risk for BRCA mutation carriers.