 ISSN 2362-0412

Genome-wide Linkage Search for Cancer Susceptibility Loci in a Cohort of non BRCA1/2 Families in Sri Lanka

Prabhavi Wijesiriwardhana [ac*], Anthony Mark Musolf [b], Joan E. Bailey-Wilson [b], Kalum Wettasinghe [c], Vajira H. W. Dissanayake [c]

[a] *Department of Medical Laboratory Science, Faculty of Allied Health Sciences, University of Ruhuna, Sri Lanka*
[b] *Computational and Statistical Genomics Branch, National Human Genome Research Institute, National Institutes of Health, Baltimore, MD 21224*
[c] *Human Genetics Unit, Faculty of Medicine, University of Colombo, Sri Lanka*

*Corresponding author: *prabhavimls@yahoo.com*

ABSTRACT

Introduction: Identification of pathogenic variants will open up an opportunity to implement surveillance and risk reducing measures that mitigate or prevent diseases. Although linkage studies have been utilized for the investigation of genetic variants associated with risk of hereditary breast cancer in many countries in the world, little is known about their role in non *BRCA1/2* individuals and their family members in the Sri Lankan population. Our objective was to identify the susceptibility loci related to the inherited risk of cancer in a cohort of Sri Lankan women affected with breast cancer. Method: Forty-eight members from four families, in which at least three individuals within third degree relatives affected by breast cancer, were selected. Genotyping using the Illumina Global Screening Array having 654,027 single nucleotide polymorphism (SNP) markers was performed. Merlin software was used to conduct two-point parametric linkage analysis with cancer at any site as the trait. An autosomal dominant model with a disease allele frequency of 1% was assumed. Penetrance was set at 90% for carriers with a 10% phenocopy rate. LOD (Logarithm Of Odds) scores were calculated for each of the four families and heterogeneity LOD (HLOD) scores were calculated across families. Results: Thirty one variants exhibited genome-wide suggestive HLODs. The top overall HLOD score was at rs1856277, an intronic variant in *MYO16* gene on chromosome 13. The two most informative families also suggested several candidate linked loci in genes, including *EXOC1*, *HUS1B*, *STIM1* and *TUSC1*. Discussion and conclusion: This study provides the first step in identifying germline variants that may be involved in risk in cancer-aggregated non-*BRCA1/2* families from the understudied Sri Lankan population. Several candidate linked regions showed suggestive evidence of linkage to cancer risk. However, additional studies are required due to low power in the existing families and probable genetic heterogeneity across families.

Keywords: *breast cancer, genotyping, hereditary cancer, linkage analysis, variants*