Genomic Analysis of familial Ovarian and Breast Cancer among Saudi Population

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INTRODUCTION

Breast cancer is the most common cause of mortality of women at the age of 40-50 year old. In Saudi women the highest age of diagnosis was between 21 to 36 years which might suggests stronger link to hereditary factors like BRCA mutations. Ovarian cancer has the highest mortality rate among gynecological cancers with high morbidity rate estimated to be the seventh most common cancer among women. The Saudi population is estimated to have the highest rate of consanguinity worldwide, and the spread of unique genetic homogeneity and Mendelianism has resulted in a higher incidence of genetic disorders, including several common types of cancer. There is not any local study that characterized ovarian cancer genetic mutation in Saudi women. We aim to identify genetics predisposing factors of familial Ovarian and Breast cancers in Saudi Population. Founder mutation identification of breast and ovarian cancers will be of great value to expedite development of screening testing the target population. Also, Identification of BRCA mutations in Saudi women will be an important intervention for the patient. Finally, we aim for (exome) genome sequencing to identify novel mutations in Saudi women and in patient with aggressive clinical features.

OBJECTIVES

To Screen the patient samples for Epithelial Ovarian and Breast Cancer (excluding borderline tumors) genes which include BRCA1, BRCA2, MLH1, MSH2

We further want to hypothesize to do whole exome sequencing on a subset of positive samples with evident mutations in BRCA1, BRCA2, MLH1, MLH2. This would enable to find other associated mutation in other physiologically related genes.

MATERIALS AND METHODS

Inclusion Criteria: Female patient with confirmed cases epithelial ovarian cancer and breast cancer patients by histopathological examination with Saudi nationality at birth, aged 18-80.

Sample storage: Sample type: K3 – EDTA blood Sample

All the samples should be stored at around 4 degrees Celsius (not frozen).

Genetic Screening: Genomic DNA extracted from whole blood is used for genetic analysis. An average of 100-200ng genomic DNA utilized. A set of specific mutations in the following genes will be studied

DNA extraction and quantification

The QIAamp DNA Mini kit is used for extraction. The extracted DNA is tested for quality and quantity on a Nanodrop spectrophotometer. The 100 nanogram quantity of DNA is used for PCR amplification.

Primer design, PCR optimization, amplification and purification

The primers specific to the polymorphisms are designed using the UCSC Human Genome Browser. Primer pairs (forward and reverse) covering a minimum of 50 bases are sent for commercial synthesis. The PCR program is finalized after several trails by a gradient PCR.

Sequence PCR, Purification and DNA Sequencing

The purified amplified products are used for setting up a sequence PCR. The Big Dye Terminator V3.1 kit from Applied Biosystems is utilized for this purpose.

RESULTS

The total number of cases collected for BRACA genetic testing are 173 cases during last 2 years (2016-2018), in which 13 cases (7.5 %) was positive for BRACA, 105 (60.6%) was negative and 55 (31.8 %) are waiting for the results. Out of the 173 cases, 96 (55.49%) was diagnosed as breast cancer, 8(4.6%) was diagnosed as ovarian-adnexal mass.

All of the cases are high risk patient for breast and ovarian cancer, 81 (46.8%) reported a history of breast cancer diagnosed at a young age (premenopausal or young than age 50), 10 (5.8%) has a personal history of triple negative breast cancer diagnosed at age 60 or younger, 6 (3.5%) has personal history of breast cancer affecting both breasts (bilateral breast cancer), 3 (1.73%) has a personal history of both breast and ovarian cancers. 9 (5.2%) had a personal history of ovarian-adnexal cancer.

CONCLUSTION

The first phase of the study was concluded, all positive BRACA genes will be further studied for a set of specific Breast cancer 1 (BRCA1), Breast cancer 2 (BRCA2), mutL homologue 1, colon cancer, nonpolyposis type 2 (MLH1) and mutS homologue 2, colon cancer, nonpolyposis type 1 (MSH2). whole (exome) genome sequencing will be conducted to identify novel mutations in Saudi women and in patient with aggressive clinical features.

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