IDENTIFICATION OF BRCA1/2 GERMLINE MUTATIONS BY INTEGRATED APPROACH

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GOALS: Germline BRCA gene mutations have been demonstrated to be associated with hereditary breast cancer and ovarian cancer. Identification of BRCA mutations would greatly improve the preventive strategies and management of breast cancer. Sanger sequencing has been the gold standard in identifying these mutations. However, 4–28% of inherited BRCA mutation may due to large genomic rearrangements (LGRs) of these genes which could be missed by using Sanger Sequencing alone. This study aims to evaluate the pick-up rate of LGRs in our cohort. Germline BRCA gene mutations have been demonstrated to be associated with hereditary breast cancer and ovarian cancer. Identification of BRCA mutations would greatly improve the preventive strategies and management of breast cancer. Sanger sequencing has been the gold standard in identifying these mutations. However, 4–28% of inherited BRCA mutation may due to large genomic rearrangements (LGRs) of these genes which could be missed by using Sanger Sequencing alone. This study aims to evaluate the pick-up rate of LGRs in our cohort. METHODS: A total of 1,463 clinically high-risk patients with breast cancer and/or ovarian cancer based on age of onset, family history of breast and ovarian cancer, tumor biological subtype including triple negative breast cancer (TNBC) were recruited through The Hong Kong Hereditary Breast Cancer Family Registry from 2007 to 2014. Full gene sequencing (either Sanger sequencing or Next-generation sequencing) and multiplex ligation-dependent probe amplification (MLPA) were performed. RESULTS: From 2007 to 2014, we identified 126 deleterious BRCA mutations in the recruited high-risk probands. A total of 56 (3.83%) gene mutations were in BRCA1 and 70 (4.78%) in BRCA2. BRCA1- positive probands had a significantly younger age of diagnosis when compared with BRCA2-positive probands (p = 0.03). The frequency of TNBC is significantly higher in BRCA-positive than in BRCA-negative probands (p = 0.0001) and TNBC are more likely to be associated with BRCA1-positive than BRCA2-positive probands (p = 0.01). Overall these LGRs accounted for 6.35% (8/126) of all BRCA mutations in our cohort, in which 8.93% (5/56) of BRCA1 mutations and 4.29% (3/70) of BRCA2 mutations. One of the mutations was de novo and only identified in proband but not in any of the family members. CONCLUSION: Through this integrated approach, both small nucleotide variations and LGR could be detected. We suggest MLPA should incorporate in the standard practice for genetic testing to avoid false negative results which would greatly affect the management of these high-risk families.