Reversion of pathogenic *BRCA1* L1780P mutation confers resistance to PARP and ATM inhibitor in breast cancer

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BRCA1 L1780P (c.5339T->C; p.Leu1780Pro; rs80357474) germline mutation is a rare pathogenic variant predominantly found in hereditary breast cancer patients in Korea. To elucidate the specific genetic properties of cancer cells carrying this mutation and exclude the complexity arising from heterogeneous cancer cell populations, we successfully established patient-derived xenograft (PDX) models and PDX-derived cell lines (PDXDC) from two different patients with the *BRCA1* L1780P mutation. Through comprehensive sequencing analyses of these samples, we observed loss of heterozygosity (LOH) events at the *BRCA1* locus in both patients. However, intriguingly, the LOH occurred in opposite directions concerning the presence of the *BRCA1* L1780P allele; one patient lost the chromosome carrying the wildtype *BRCA1* allele, while the other lost the chromosome with the L1780P allele. This reversion mutation resulted in the loss of the mutated allele, retaining only the wildtype allele, potentially leading to resistance against drugs targeting homologous recombination deficiency (HRD), such as PARP or ATM inhibitors. Our HRDetect and CHORD analyses, which are well-known methods for predicting HRD status, revealed a strong association between the specific *BRCA1* L1780P mutation and HRD, distinguishing it from other *BRCA1* mutations that do not exhibit such a correlation. Notably, we demonstrate that PARP inhibitors (PARPi) and ATM inhibitors (ATMi) are effective treatments for *BRCA1* L1780P mutant cancer, with the combination therapy showing even greater efficacy. However, we also identified drug resistance in the case of the reversion mutation despite the high HRD prediction scores. Therefore, exercising caution is recommended when utilizing HRD prediction for designing personalized treatment strategies for breast cancer patients with *BRCA1/2* mutations.