In about 25% of cases, hereditary breast and ovarian cancer (HBOC) is caused by mutations in the BRCA1 or BRCA2, both components of DNA repair pathways. In recent years, additional genes of the DNA repair system such as CHEK2, ATM, BRIP1, PALB2, RAD51C and others have been implicated in HBOC. Interestingly, many of these genes had been identified first (with biallelic mutations) in Fanconi Anemia patients. We set out to study the contribution to HBOC of 30 DNA repair genes contained within the TruSight Cancer panel (Illumina).

All 300 patients fulfilled the inclusion criteria defined by the German Consortium for Breast and Ovarian cancer. Target enrichment was performed with the Illumina TruSight cancer panel which includes 94 genes associated with a predisposition towards cancer.

Next generation sequencing data were generated on a MiSeq (Illumina). Variants were identified and analysed by GensearchNGS software (PhenoSystems). Copy number variation analysis was carried out with the NextGENe CNV detection tool (Softgenetics).

A variant of uncertain significance (VUS) was identified in at least 1 of the 30 genes tested in 147 individuals (49%), for a total of 193 variants. CNV analysis revealed deletions or duplications only in BRCA1 and not in any of the other genes studied.

Mutation screening by NGS was able to identify monoallelic, likely pathogenic mutations in DNA repair genes other than BRCA1/2 in a significant number of HBOC cases. However, the causative association to HBOC and the prospective tumor risks for many of these mutations and genes have yet to be determined. Of note, extending the analysis to a larger number of genes proportionally increases the number of unclassified variants and the workload to survey and classify them.