WHOLE EXOME SEQUENCING IN A FOUNDER POPULATION IDENTIFIES NOVEL OVARIAN CANCER SUSCEPTIBILITY LOCI

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Ovarian cancer is a lethal gynecologic malignancy of heterogeneous cellular origin and presentation. However, less than 40% of ovarian cancer heritability is known. Massively parallel whole exome sequencing (WES) enables the detection of rare, intermediate-risk variants (odds ratio 2.0-5.0). We performed WES in germline DNA of 96 Jewish women with ovarian cancer without BRCA1 or BRCA2 mutations. Nimblegen's SeqCap EZ Exome Library kit v2.0 was used to generate the Illumina sequencing libraries. The capture probes target approximately 20,000 RefSeq genes composed of approximately 30,000 transcripts and 300,000 exons. The total size of the target region was 36.5 Mb, and the total capture region was 44.1 Mb. The average per sample coverage was greater than 150x, with an average of 91% of target bases covered at 20x. Reads were mapped to the human reference genome (hg19) using the Burrows-Wheeler Aligner (BWA) to generate SAM files. Reads were recalibrated and realigned using the Genome Analysis Tool Kit (GATK). We identified 287 mutations classified as likely deleterious, including frameshift, stopgain, splicing and indels mutations in 200 genes. No frameshift mutations were detected in BRCA1/2 (as expected), MLH1, MSH2, RAD51D, or PPM1D. Nor did we detect RAD51C, BRIP1 or PALB2 truncating mutations in agreement with previous reports in Jewish women. Ten of the novel genes with mutations are known interactors of BRCA1, while three of the novel genes interact with BRCA2. A further ten genes with mutations are nuclear mitochondrial genes. Two genes with mutations previously reported in breast cancer showed mutations in Jewish ovarian cancer: NEIL1 and MLL4. The utilization of a founder population greatly facilitated the identification of novel ovarian cancer susceptibility genes characterized by rare variation conferring an intermediate risk of ovarian cancer.