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Next-generation sequencing for diagnosis of patients with hereditary breast and ovarian cancer

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BRCA1 and *BRCA2* genes are the two most commonly mutated genes in families with Hereditary Breast and Ovarian Cancer (HBOC). However several additional breast cancer predisposition genes are now known to be associated with HBOC. Parallel sequencing of these multiple genes is possible with customized next generation sequencing panels. In the present study we evaluated twenty breast cancer patients with positive family history of breast and ovarian cancer were subjected to high throughput next generation sequencing panel testing. Genes analyzed in the panel are *ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1,MRE11A,MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, STK11* and *TP53*. Mutations identified by NGS were validated using Sanger sequencing. Software analyses by Polyphen-2, SIFT, Mutation Taster and Align-GVGD was done to predict damaging effect of novel variants. Predictive genetic testing and counseling was done for the first degree relatives. Pathogenic mutations in 7 out of 20 patients (35%) were identified. In rest of the seven patients we found several variants of unknown significance (VUS). Four patients had mutations in BRCA1 gene (c.5074+1G>A, c.4484+1G>A, c.4552C>C/T p.Q1518Ter, c.7480C>T; R2494X) and one patient had mutation in BRCA2 gene (c.9215T>A p.Val3072Glu). One of the patients had a novel nonsense mutation in MRE11 gene (c.1090C>T: p.Arg364Ter). Another patient was a double heterozygote for mutations in *MSH6* and *BARD1* gene. *In silico* analysis, segregation study in the family and 100 normal controls were studied to confirm the pathogenicity of novel mutations. Multi-gene parallel sequencing allowed more effective and accurate diagnosis of HBOC families and supports incorporation of panel testing into clinical practice. Clinical genetic counseling for patients with novel variants and VUS in intermediate penetrance gene is complex and challenging and further studies are needed to clarify the precise management of these patients.

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Molecular profiling of genetic alterations in prostate cancer patients from Northern India

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Molecular categorization of cancer based on specific genetic alterations and emergence of high-throughput technologies has led to recent advances in personalized medicine for the treatment of cancer. The seminal discovery of the gene rearrangement involving the androgen-regulated gene trans-membrane protease, serine 2 (*TMPRSS2*) with erythroblastosis virus E26 transformation-specific (*ETS*) transcription factor family (*ERG, ETV1, ETV4* or *ETV5*) which is recurrent in ~50% of the prostate cancer (PCa) patients formed the basis for classification of the disease by distinct molecular subtypes. These molecular sub-types based on genetic aberrations including ETS, RAF gene-rearrangements, *PTEN* deletion and SPINK1 (serine peptidase inhibitor, Kazal type-1) over-expression showed clear prognostic and diagnostic value; however prevalence of these molecular alterations is largely unknown for the Indian PCa patient population. Here, we provided the first comprehensive report about the prevalence of the major causal aberrations in Indian PCa samples which include *ERG, ETV1, ETV4* and *RAF* kinase genetic rearrangements, SPINK1 over-expression and *PTEN* deletions. Our findings suggest that ERG is highly recurrent (~49%) gene rearrangement among Indian PCa patients; furthermore, *ETS* gene rearrangement and SPINK1 over-expression patterns in Indian PCa cohort largely resembled those observed in Caucasian population but differed from Japanese and Chinese patients. The molecular sub-type data for Indian PCa patients could aid in early diagnosis and clinical decision-making for the pursuit of targeted therapy.

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