Genome sequencing provides diagnostic confirmation of hereditary breast cancer beyond *BRCA1/2* mutation detection in Kenyan patients

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Introduction: As genetic research gains momentum in Africa the ability to obtain true informed consent and implementation of effective feedback strategies become increasingly important. Screening for causative *BRCA1/2* mutations in germline DNA samples of Kenyan patients recruited at the Moi Teaching and Referral Hospital was found to be inadequate. Application of advanced technologies such as whole exome sequencing (WES) may be more appropriate to identify high-risk patients for risk reduction intervention.

Objective: To determine the spectrum of mutations in breast cancer susceptibility genes in Kenyan patients selected for WES based on family history and tumour pathology.

Methods: A total of 96 (94 women and 2 men) histologically confirmed breast cancer patients were consecutively enrolled in this study (Ethics approval number 000655). DNA was extracted from saliva samples of 13 patients aged 35-70 years. Eight patients with a family history of cancer and five with triple negative breast cancer were subjected to whole exome sequencing (WES) using the Ion Proton. WES reads were mapped to the GRCh37 human reference genome and variants called with the Torrent Suite. A total of 28 genes (including *BRCA1/2)* were prioritized for variant classification using international guidelines.

Results: Pathogenic/ likely pathogenic mutations were identified in the *BRCA2* (c.5159C>A: p.S1720X), *NBN* (c.175C>T: p.Q59X), *TP53 (c.-232G>C),* and *MSH2* (*c.380A>G; p.N127S)* genes. Several variants of uncertain clinical significance (VUS) were also identified, including 6 VUS in *ATM*, 5 each in *BRCA2* and *RECQL*, 3 in *BRCA1* and *RAD50*, 2 each in *PMS1, BARD1* and *MLH1*, and one each in *TP53, CHEK2, EPCAM, MRE11A, MSH6, NBN, RAD51B, RAD51C,* and *RAD51D.*

Conclusion: Germline pathogenic mutations were identified in 30.8% of the study cohort, of which 23.2% were identified in genes other than *BRCA1/2*. With the rise of more affordable high throughput testing technologies, comprehensive multi-gene testing may become a reality in Kenyan breast cancer patients with the aim to facilitate clinical management and cancer prevention in a familial context.