Integrating germline and tumour genetics towards individualised oncotherapy in South African breast cancer patients

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Background: Risk management of breast cancer involves a complex process spanning the continuum of care from early-stage to metastatic cancer and survivorship. Targeted next-generation sequencing (NGS) technology is driving personalised medicine in oncology practice. Integration of findings related to both the somatic genome that determines prognosis and the tumour's response to therapy, as well as the germline genome that governs treatment exposure and toxicity, is challenging.

Aim: To evaluate the potential benefit of combining whole exome sequencing (WES) using germline DNA with tumour genetics in South African breast cancer patients.

Methods: Germline WES was performed in DNA samples of 14 breast cancer patients based on 1) *BRCA1/2* (founder) mutation status, 2) tumour pathology and 3) response to treatment after obtaining informed consent (Ethics reference number N09/08/224). Two patients with treatment-resistant breast cancer were previously screened for cancer hotspot mutations using targeted sequencing of DNA extracted from solid tumours, and four patients with early-stage breast cancer had microarray testing to determine recurrence risk. Functional variants (Ion Proton) were prioritised against a primary set of known breast cancer driver genes, followed by a secondary set of genes frequently mutated in tumour DNA (~500 genes). Potential disease-causing variants were verified with the Integrative Genomics Viewer and confirmed with Sanger sequencing. The CNVkit program was used to detect copy number variants (CNVs).

Results: Three protein truncating (*BRCA2*:R18Lfs *and* L1294X*; PALB2*:D434fs) and 2 missense (*RAD50*:R385C*; TP53*:N340D) variants were detected in known breast cancer driver genes. Detection of both a pathogenic *CDH1* c.1587dupT (p.A530Cfs) mutation and likely pathogenic *CHEK2* c.232C>T (p.Q78X) mutation in the same patient was compatible with mixed invasive lobular (pleomorphic type, > 90%) and (ductal) carcinoma of no special type (< 10%). *CYP2D6*4* was identified as an important inherited factor that could alter drug metabolism in a tamoxifen-resistant patient with the *BRCA2* c.51_52delAC (p.Arg18Leufs) mutation.

Conclusion: WES enabled identification of genetic markers relevant to both cancer development and tailored therapeutic intervention in a single genetic test. Confirmation of WES results by comparative genetic testing using standard methodology contributed to the analytical validation of the test.