



## New recurring *BRCA1* variant: An additional South African founder mutation?

**To the Editor:** Hereditary breast and ovarian cancer syndrome (HBOC) caused by pathogenic variants in the *BRCA1* or *BRCA2* genes accounts for 15 - 20% of the hereditary component of breast cancer.<sup>[1]</sup> Comprehensive genetic testing of the *BRCA1* and *BRCA2* genes remains costly in South Africa (SA) owing to the expense of high-throughput technologies such as next-generation sequencing (NGS) and the complexities of downstream analysis and variant interpretation. Targeted testing for a subset of variants may be considered as a first-line test in specific population groups, particularly in resource-limited settings. In SA, patients with Afrikaner heritage may initially be tested for the three known Afrikaner founder mutations.<sup>[2]</sup> If this initial screen is negative or patients are not of Afrikaner ancestry, comprehensive testing through NGS is recommended.

Full sequencing of the *BRCA1* and *BRCA2* genes is available either through an in-house NGS assay or through an international referral service to Invitae laboratory in the USA. Since 2015, we have identified eight seemingly unrelated individuals with a *BRCA1* sequence variant: *BRCA1* c.45dupT (p.Asn16\*). All these individuals were of Afrikaner ancestry (either self or clinician reported). Five of them were identified through PathCare in-house testing and 3 by Invitae laboratory. This variant has previously been reported only once in the literature, in a single Afrikaner individual tested by the National Health Laboratory Service in Johannesburg.<sup>[3]</sup>

This *BRCA1* variant is not present in population databases (Exome Aggregation Consortium: no frequency) and has a single Invitae entry on ClinVar (RCV000691259). This sequence change, an insertion of a tyrosine molecule in exon 2 of the *BRCA1* gene, results in a premature translational stop signal and is expected to result in an absent or disrupted *BRCA1* protein. As this is a loss-of-function change, this variant has been classified as pathogenic.

Given the shared ethnic background of the patients in whom this variant has been detected, we propose that the *BRCA1* c.45dupT pathogenic variant may be another Afrikaner founder mutation in the SA population. Including this variant in first-line founder mutation screening may reduce testing costs to patients and identify those at risk for HBOC without the need for comprehensive testing. Additional research into the frequency and distribution of this variant in the SA population is warranted.

Ethics approval has been obtained from the Health Sciences Research Ethics Committee of the University of the Free State (UFS-HSD2019/0484/2805).

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