INVESTIGATING THE GENETIC AETIOLOGY OF HERITABLE CONNECTIVE TISSUE DISORDERS IN SOUTH AFRICA USING NEXT-GENERATION SEQUENCING (NGS).

Heritable connective tissue disorders (HCTDs) are a heterogeneous group of disorders affecting the connective tissue. They are caused by pathogenic variants in genes that encode proteins in the extracellular matrix or the post-translational modifications thereof. There is a wide phenotypic spectrum and extensive overlap in the clinical features of the different HCTDs. For these reasons, making a definitive clinical diagnosis is difficult.

Currently in South Africa, the diagnosis of HCTDs is achieved using clinical assessments and available diagnostic criteria. However, these may not always assist because many physical manifestations of HCTDs are age-dependent in their penetrance making diagnosis challenging in young individuals. This study aimed to determine the value of a targeted Next-Generation Sequencing (NGS) panel for known HCTDs genes in the molecular diagnosis of these disorders.

Fifteen (15) patients with a clinical diagnosis of one of seven selected HTCDs were invited to participate in the study. Automated DNA Library, template preparation and sequencing were executed using the Ion Torrent™ system. The Ion Torrent Suite™ and Ion Reporter™ software, as well as the Ensembl Variant Effect Predictor tool were used for variant calling and annotation, respectively.

Six different putative disease-causing variants were identified in 12 family entities, yielding a mutation detection rate of 50%. Two of these variants are novel, contributing to the mutation spectrum of HCTDs. With the use of NGS, we confirmed and established the diagnosis in our cohort, and we recommend its use in a diagnostic setting.

Keywords: Marfan syndrome, Fibrillin-1, Next-Generation sequencing.