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Smal, Clarice

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INVESTIGATING THE GENETIC AETIOLOGY OF RASOPATHIES IN A COHORT OF AFRICAN PATIENTS

The RASopathies are a group of genetic disorders with clinical overlap caused by germline pathogenic variants in genes of the RAS/MAPK pathway. Limited studies have been done in African populations and therefore the genetic aetiology of RASopathies remain poorly understood in individuals of African ancestry. Furthermore, there is currently no routine molecular diagnostic testing available for patients with a RASopathy in the State sector of South Africa. This study formed part of a larger investigation that used a custom designed targeted NGS gene panel to determine the genetic cause of RASopathies in South Africa and offer better diagnostic services to these patients. The primary study had a diagnostic yield of 56.6% which left a large proportion of the patient cohort without a genetic diagnosis. Additional molecular approaches using MLPA and WES were investigated in the current study to establish a molecular profile for the patients in whom no pathogenic disease-causing variants were identified and to determine whether MLPA and WES could improve the diagnostic yields for South African patients with a RASopathy. MLPA identified three deletions in three patients clinically diagnosed with Neurofibromatosis type 1 achieving a diagnostic yield of 25.0%. This included one multi-exon and two large deletions encompassing the whole *NF1* gene as well as flanking genes. WES identified two pathogenic and one likely pathogenic disease-causing variants in three patients achieving a diagnostic yield of 37.5%. Two of these variants were associated with rare developmental disorders unrelated to the RASopathies and changed the clinical diagnosis of the patients. The other variant was present in a known RASopathy gene not included on the targeted NGS panel. This study significantly improved the diagnostic rate for patients suspected of having a RASopathy and provides insight into improving genetic testing for patients in South Africa. Overall, this study demonstrated the value of reflex testing using both MLPA and WES in a South African setting.