Abstract

With Next Generation Sequencing (NGS), technologies it is now possible to screen a large number of genes simultaneously through massively parallel sequencing, significantly reducing costs and time generally associated with mutation screening. After an informal survey of the diagnostic needs of the clinicians in the Division of Human Genetics, National Health Laboratory Service (NHLS), it was established that the aetiology of genetic disorders called facial dysostoses, RASopathies and Cohesinopathies (FRASC) could be understood better using NGS. These are developmental disorders that are phenotypically different and are commonly referred to our genetic clinic, currently there is limited genetic testing for these conditions in South Africa. A NGS panel targeting genes associated with the FRASC disorders was designed and optimised. Upon successful optimisation the panel was then utilised to sequence samples from patients presenting with features suggestive of RASopathies. An overall detection rate of 56.6% (34/60) was obtained for all RASopathy patients sequenced in the current study. Detection rate of 46.7% (7/15) for neurofibromatosis type 1 (NF1) patients and 60% (27/45) for patients with non-NF1 RASopathies was obtained. No clinically significant variants were identified in 26 of the 60 patients (43.3%), two of the 26 had a VUS in the *MAP2K1* gene. Seven patients of the panel negatives were successfully sequenced using whole exome sequencing (WES), one patient had a pathogenic variant and the rest had variants of uncertain significance identified. This is the first report profiling mutations and clinical features in patients with RASopathies as a whole in South Africa, compared to a study focusing on NS patients only. The detection rates obtained were comparable to other international studies using NGS, except for detection rate of *LZTR1* and *BRAF1* gene variants observed in Noonan syndrome patients. The (35/60) 58.3% (panel and WES) of patients with a disease causing variant identified in this study now have a molecular confirmation that they previously did not have. Our results show that a targeted panel could be an effective first-line diagnostic testing for RASopathies in SA. The development of the multi-disease targeted panel in the current study has contributed to the design of the 500 gene inherited disease NGS targeted panel (IDP) that is currently being utilised in our facility for diagnostic testing of various monogenic disorders.