Introduction

Noonan spectrum disorders (NSDs), also known as RASopathies, are caused by genetic defects that impact the RAS-mitogen-activated protein kinase (MAPK) intracellular signaling pathway. They are pediatric disorders that share a common spectrum of symptoms, including congenital heart defects, distinctive craniofacial features, cutaneous abnormalities affecting skin and hair, and developmental tumors, both benign and malignant cancers. The most common is Noonan syndrome, with a prevalence of 1:1000–1:2500 births.

Because NSDs present with a phenotypic spectrum, testing for individual candidate genes can become an iterative, time-consuming process. Multi-gene genetic tests have become more widely available, and Invitae offers customized panels and a variety of pre-curated panels for NSDs. We use next-generation sequencing (NGS) for read-through sequence and copy number analysis for detecting variants. A score-based system developed at Invitae (Sherloc, Figure 3) is used in the interpretation of observed variants that are reported with a five-tier classification for clinical assessment.

Analysis of orders received to date at Invitae for genes and/or panel testing was evaluated for clinical indication(s) provided by the ordering clinicians. This analysis was used to understand the relationship between clinical indication(s) and genes/panels tested as well as the value of panel-based genetic testing for NSDs. For example, most clinicians have ordered the Noonan spectrum disorders panel of 12 genes (BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, SHOC2, SOS1, and SPRED1), but in 43% of orders, the NF1 gene was also selected for testing. In 5% of the tests ordered, the clinical indication was hypertrophic cardiomyopathy (HCM), which included testing of the 12 NSD panel genes and 16 genes on the Invitae HCM panel. For the majority of tests ordered (92%), the clinical indication phenotypes included short stature, facial dysmorphism, heart defect, and other features that fit the wide spectrum of NSDs. In 34.6% of cases, a likely pathogenic or a pathogenic variant was identified; in 9% of cases, a variant of uncertain significance (VUS) was identified, and 56% were negative reports.

Methods

Our customers can choose tests either based on predesigned gene panels or they can design a custom test that includes panels and add additional genes they suspect could harbor variants explaining the clinical phenotypes observed in their patients. In this analysis, we analyzed all orders received from January 2014 to May 2015 for our Noonan spectrum disorders panel, which includes genes BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, SHOC2, SOS1, and SPRED1. The final set of ordered genes, which include additional genes chosen for testing, are compared with the standard Noonan syndrome spectrum disorder panel across the testing indication provided by the ordering clinicians. We considered positive reports when pathogenic and likely pathogenic variants were detected; VUS reports when only one or more VUS was detected, and negative reports when only likely benign and benign variants were found in the patient.

Results

For example, the most common condition was Noonan spectrum disorders (NSDs), also known as variants were found in the patient.

Conclusions

An analysis of genetic tests of Noonan spectrum disorder genes and panels over an 18-month period was performed to understand the relationship between clinical indications, genes tested, and results obtained. In majority of cases (87%), the 12-gene NSD panel was selected when the clinical indication was for various Noonan features. In 6% of cases, there was either a confirmed Noonan or suspected Noonan diagnosis indicated, and in 1% Costello syndrome was suspected. NF1 was a frequent add-on gene to the NSD panel with clinical observation of café au lait spots in addition to various Noonan features.

Analysis of positive and negative findings in Table 2 shows that when the NF1 gene was added, a positive finding was observed in 34% of reports, and as expected, variants in the PTPN11 gene accounted for the majority of positive reports in the NSD panel.

Overall, a pathogenic or a likely pathogenic variant was identified in 35% of tests and in 56%, no reportable variants were identified.