To reflex or not to reflex: genetic testing patterns for neurofibromatosis 1 (NF1) and Legius syndrome

Amanda Bergner, MS, CGC, *Ambry Genetics*

Background: Germline molecular testing for NF1 and Legius syndrome using next generation sequencing (NGS) and deletion/duplication analysis (del/dup) is being offered by an increasing number of diagnostic laboratories. Clinicians now have the option to pursue testing for one or both of these genes, concurrently or sequentially, using one or both testing methodologies. It is unclear what testing patterns for *NF1* and *SPRED1* are most prevalent, and what the comparative detection rates are for various approaches.

Methods: All sequential cases submitted to one lab for germline genetic testing of *NF1* and/or *SPRED1* by any testing methodology in any sequence between January 2014 and December 2016 were retrospectively reviewed. Cases in which a gene mutation was identified were selected and reviewed.

Results: 597 probands underwent testing: 53.2% (318) were tested only for *NF1*, 5.4% (32) were tested only for *SPRED1*, and 41.4% (247) were tested for both. Of the probands tested for both, 15.4% (38) underwent concurrent NGS and del/dup of both genes, 30.4% (75) underwent NGS for *NF1* and *SPRED1* with reflex to del/dup of both, and 54.2% (134) underwent NGS and del/dup for *NF1* with reflex to NGS and del/dup for *SPRED1*. The overall detection rate was 33.3% (199/597), with mutations in *NF1* accounting for 97.0% (193/199). NGS detected 92.5% (184/199) of all mutations, with the remainder identified by del/dup. Specific detection rates for all probands undergoing *NF1* NGS was 32.3% (178/551), *NF1* del/dup was 2.9% (15/522), *SPRED1* NGS was 2.5% (6/238), and *SPRED1* del/dup was 0% (0/218).

Discussion: As the options for molecular interrogation of *NF1* and *SPRED1* increase, clinicians must ensure that they are ordering relevant testing that is most likely to detect a mutation, if present. Although most mutations in this cohort were detected using NGS, an important minority of NF1 cases were identified using del/dup, underlining the need for both methodologies to achieve maximum detection rates. Del/dup for *SPRED1* appears less relevant. Interestingly, there was no significant difference in detection rates for first-round testing if a reflex from *NF1* NGS and del/dup to *SPRED1* NGS was ordered or if a reflex from *NF1* and *SPRED1* NGS to *NF1* del/dup was ordered. For individuals who have clinical features consistent with both NF1 and Legius, there may be no benefit to selecting one sequence over the other. This is particularly relevant when insurance coverage, not clinician preference, dictates the type of testing that can be ordered.

Full List Authors: Patrick Reineke, Ambry Genetics; Zoe Powis, MS, CGC, Ambry Genetics