**Diagnosing NF1 using multi-gene cancer panels: an emerging trend and the implications for NF clinicians**

**Amanda Bergner, MS, CGC,** *Ambry Genetics*

**Background:** Historically, individuals referred to an NF clinician for consideration of neurofibromatosis 1 (NF1) have presented with clinical features consistent with NF1, a family history of NF1, or both. As next-generation sequencing (NGS) is becoming more widely available, a distinct pattern of referral for NF1 clinical evaluations is emerging. The gene for NF1 (*NF1*) is now included on a variety of multi-gene cancer panels, and individuals are being referred for an NF1 clinical evaluation *after* receiving a genetic diagnosis of NF1. This trend is significant for both clinicians who are managing this new type of referral and individuals who are receiving an unexpected diagnosis of NF1 through genetic testing for cancer in adulthood.

**Methods:** All sequential oncology cases submitted to one lab for germline genetic testing panels containing *NF1* between July 2015 and December 2016 were retrospectively reviewed. Cases with an *NF1* gene mutation or variant of uncertain significance (VUS) were identified, and available clinical data and genetic test results were reviewed. Follow-up clinical correlation evaluations at a major NF Center were conducted for several cases.

**Results:** 100 cases were found to have an *NF1* mutation, 77% of which presented for testing due to a personal and/or family history of breast cancer. 42% had no reported clinical features or family history of NF1 and 16 (38.1%) of these cases received mosaic test results. The average age at testing for cases with mosaic results was 67.3 years (45-81) and for non-mosaic results was 48.8 years (19-75). 8/100 cases were also found to have a mutation in a separate known cancer gene. 1217 cases were found to have an *NF1* VUS. 4 probands were evaluated for clinical correlation at a major NF Center, which confirmed the diagnosis of NF1 for 2; both had received non-mosaic mutation results. The other 2 cases were not found to have clinical features of NF1; one had a VUS test result and the other had a mosaic mutation result.

**Discussion:** This new type of referral presents many challenges to the NF clinician, including managing the unexpected nature of the diagnosis later in life, determining the relationship (or lack thereof) between a variety of cancers and NF1, and discussing the heritable nature of NF1 after child-bearing has already occurred. In addition, this data highlights the need for NF clinicians to understand more about the interpretation of *NF1* genetic testing results, including 1) distinguishing between mutations and variants of uncertain significance, 2) interpreting mosaic test results, 3) correlating clinical symptoms with test results, and 4) recommending follow-up genetic testing, as appropriate. Given the source of these new referrals, ongoing education of our oncology colleagues about the primary features of NF1 and when to refer patients to an NF specialist will become important.

Full List Authors: Kaleb Yohay, MD, NYU Langone Medical Center; Zoe Powis, Ambry Genetics; Kara Anstett, MS CGC, NYU Langone Medical Center