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

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Background

- Historically, individuals referred to an NF clinician for consideration of a neurofibromatosis 1 (NF1) diagnosis present with clinical features consistent with NF1 and/or a family history of NF1
- 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 many multi-gene cancer panels, and individuals are being referred for an NF1 clinical evaluation ***after*** receiving a genetic diagnosis of NF1
- We report data from a single diagnostic laboratory regarding the detection rate of *NF1* mutations on cancer panels, as well as clinical correlation data for several cases

Methods

- All sequential germline multi-gene cancer panels containing *NF1* ordered from one lab between July 2015 and December 2016 were identified

Multi-Gene Panel	Indication(s)
PGLNext	Paraganglioma/pheochromocytoma
OvaNext	Ovarian cancer
BreastNext	Breast cancer
CancerNext, CancerNext-*Expanded,* CustomNext-*Cancer*	Brain, breast, colon, ovarian, pancreatic, prostate, renal, uterine, and many other cancers

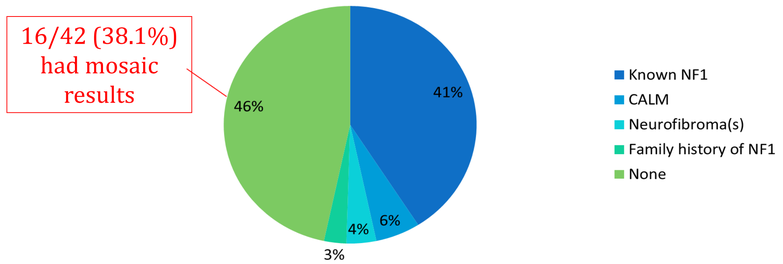
- Cases with an *NF1* gene mutation or variant of uncertain significance (VUS) were identified, and available clinical and genetic test data were reviewed
- Follow-up clinical correlation evaluations at a major NF Center were conducted for several cases

Demographics

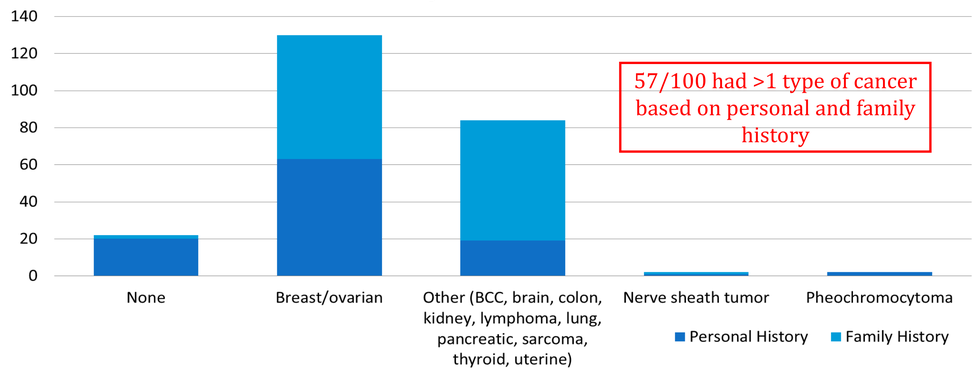
100 cases (0.001%) had an *NF1* mutation
- 7 males and 93 females
- Average age at testing was 50.9 years

Genetic Testing Results

Features of NF1 for *NF1*-Positive Cases



Cancer History for *NF1*-Positive Cases



7 cases with an *NF1* mutation also had a mutation in a separate known cancer gene

Other Cancer Gene	*NF1* Gene
BRCA1 mutation	*NF1* mutation
BRCA2 mutation	*NF1* mutation
BRCA2 mutation	*NF1* mutation - mosaic
CHEK2 mutation	*NF1* mutation - mosaic
PALB2 mutation	*NF1* mutation - mosaic
RAD50 mutation	*NF1* mutation
RAD50 mutation	*NF1* mutation

Clinical Correlation Results

4 female probands between 40-58 years were evaluated for clinical correlation at a major NF Center

Clinical History	Genetic Result	Evaluation Result
Personal history breast cancer and features suspicious of NF1	*NF1* mutation	Confirmed diagnosis of NF1
Family history multiple cancers and personal history features suspicious of NF1	*NF1* mutation	Confirmed diagnosis of NF1
Personal history breast cancer and hyperpigmented skin lesions, family history other cancers	*NF1* VUS	No features consistent with NF1, skin lesions unrelated to NF
Personal history endometrial and metastatic thyroid cancers	Low level mosaicism for *NF1* mutation	No features consistent with NF1, referred to Oncology for evaluation of heme malignancy

Take-Home Points

Almost half of all cases with an *NF1* mutation had no known diagnosis or features of NF1.

Clinical implications of this data include:
- Assist patients to manage the unexpected nature of the diagnosis later in life
- Determine the relationship (or lack thereof) between a variety of cancers and NF1
- Discuss the heritable nature of NF1 after child-bearing has already occurred.

Educational implications of this data include:
- Distinguish between mutations and VUSs
- Interpret mosaic test results
- Correlate of clinical symptoms with test results
- Recommend follow-up genetic testing, as appropriate
- Educate oncology colleagues about the primary features of NF1 and when to refer patients to an NF specialist