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The Results are in: Who is Testing Positive for *NF1* on Hereditary Cancer Multi-Gene Panels?

Zöe Powis, Holly LaDuca, Amanda Bergner, Pia Summerour, Brigette Tippin Davis

BACKGROUND

- Neurofibromatosis 1 (NF1) is one of the most common neurogenetic conditions, affecting about 100,000 children and adults in the United States (1)
- Traditionally, individuals with NF1 were identified by physical features and/or family history (2).
- Benign and malignant neoplasms are a recognized component of NF1, including an increased breast cancer risk and mobility (3-7).
- Due to the increased risk and recommended screening guidelines, the *NF1* gene is included on a variety of hereditary cancer multi-gene panels (MGPs).
- Consequently, increasing numbers of individuals with a personal or family history of hereditary cancer are undergoing *NF1* testing who may not have a NF1 clinical diagnosis.

METHODS

- 108,883 sequential cases submitted for germline hereditary cancer NGS based MGPs that included *NF1*, between May 2012 and September 2016, were retrospectively reviewed.
- *NF1* was included in MGPs associated with risk for breast cancer, ovarian cancer, paragangliomas and/or pheochromocytomas, or a pan-cancer panel.
- Sanger sequencing was performed for any regions missing or with insufficient read depth coverage for reliable heterozygous variant detection. Reportable small insertions and deletions, potentially homozygous variants, variants in regions complicated by pseudogene interference, and single nucleotide variant calls not satisfying 100x depth of coverage and 40% het ratio thresholds were verified by Sanger sequencing.(8)
- Gross deletion/duplication analysis of *NF1* using the multiplex ligation-dependent probe amplification (MLPA) kit was also performed
- Analysis of variants was conducted as previously described (9).
- All cases with a pathogenic or likely pathogenic alteration (PA) in *NF1* were identified and clinical history information (from test requisition forms and medical records/pedigrees, if provided) was reviewed.
- History of NF1 and clinical features of NF1 were specifically analyzed.
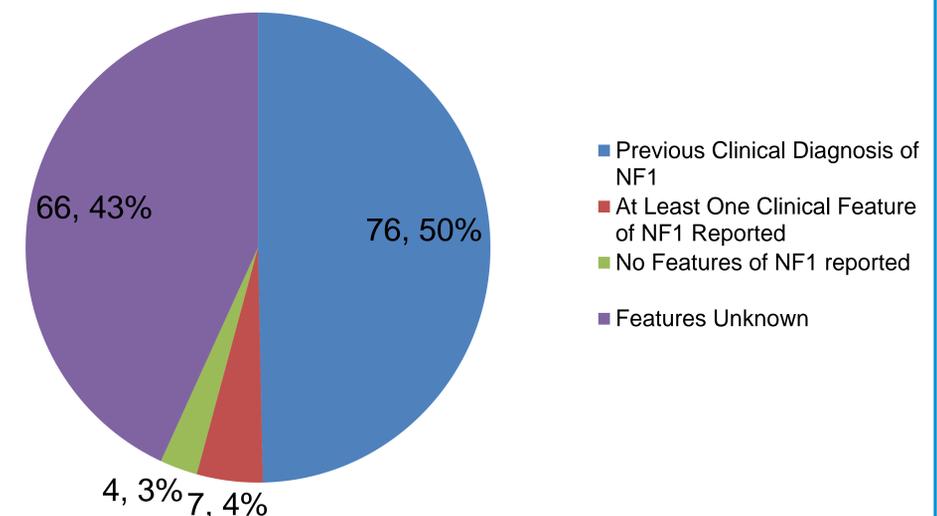
RESULTS AND DEMOGRAPHIC INFORMATION

- 153 of 108,883 (0.1%) of cases were identified with a pathogenic or likely pathogenic alteration in *NF1*.
- 141/153 (92.2%) of these cases were in females
- The average age at testing was 51.3 years
- 124 (83.8%) individuals reported a personal history of cancer (of those in which history was reported), the most common being breast cancer
- Ages of first breast cancer diagnosis:
  - Twenties - 1.1%
  - Thirties - 19.6%
  - Forties - 32.6%
  - Fifties - 26.1%
  - Sixties - 20.6%
- In 19 cases, the pathogenic or likely pathogenic alteration in *NF1* had mosaic findings
- 10 cases also had co-occurring pathogenic or likely pathogenic alterations in other cancer genes.

PERSONAL CANCER HISTORY IN INDIVIDUALS WITH PATHOGENIC OR LIKELY PATHOGENIC *NF1* ALTERATIONS
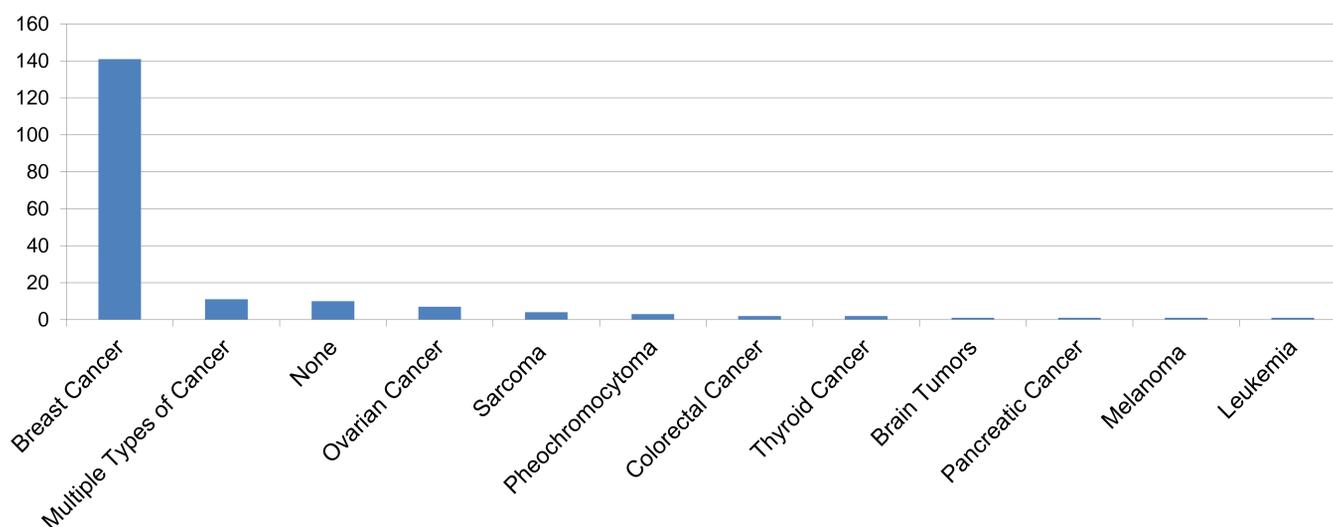
REPORTED NF1 FEATURES OF CASES WITH PATHOGENIC OR LIKELY PATHOGENIC *NF1* ALTERATIONS (n=153)

- Previous Clinical Diagnosis of NF1 — 76, 50%
- At Least One Clinical Feature of NF1 Reported — 7, 4%
- No Features of NF1 reported — 4, 3%
- Features Unknown — 66, 43%

CASES WITH MOSAIC *NF1* PATHOGENIC OR LIKELY PATHOGENIC ALTERATIONS (n=19)

- 19 cases total, all with no reported clinical features of NF1
- 17 (89.5%) with a personal history of cancer
  - 15/17 (%) with a personal history of breast cancer
    - Average age of primary diagnosis 59.5 years
  - 2/17 (%) with a personal history of uterine cancer
    - Average age of primary diagnosis 54.5 years
- All individuals are females, all with a reported family history of cancer
- The average age at testing was 64.4 years
- Four of these cases also had co-occurring pathogenic or likely pathogenic alterations in an additional gene: *BRCA2* (1), *CHEK2* (2) and *PALB2* (1)
  - One of these individuals had a maternal and paternal family history of cancer

MULTIPLE MUTATION CARRIERS

Additional Gene	Number of Cases
ATM	1
BRCA1	2
BRCA2	3
BRIP1	1
CHEK2	2
PALB2	1

- 10/153 (6.5%) of cases had a dual diagnosis of a pathogenic or likely pathogenic *NF1* alteration and pathogenic or likely pathogenic alteration in an additional gene
- 2/10 (20%) cases reported a previous NF1 clinical diagnosis
- 4/10 (40%) had mosaic *NF1* findings, no other genes had mosaic findings
- All individuals had a personal history of cancer
- 80% personal history of breast cancer, 10% uterine cancer, 10% pancreatic cancer
- Average age of breast cancer diagnosis is 53.6 years

TAKE-HOME POINTS

- This study indicates that hereditary cancer MGPs are utilized for a subset of patients with a known clinical NF1 diagnosis.
- Patients without a clinical diagnosis of NF1 may also test positive for *NF1* pathogenic or likely pathogenic alterations on hereditary cancer MGP testing and would benefit from further screening and genetic counseling.
- *NF1* carriers may also test positive for a pathogenic or likely pathogenic alteration in a second cancer susceptibility gene.
- **Clinical correlation is recommended for all cases with pathogenic or likely pathogenic alterations detected in *NF1*, particularly with mosaicism, and/or multiple mutations and further research is needed to explore these correlations to inform clinical management for individuals identified by MGP testing.**

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