High-prevalence of NF1 pathogenic variants in cancer patients without classic features of Neurofibromatosis type 1

A. Koutras[1], K. Papazisis[2], I. Boukovinas[3], R. Iosifidou[4], I. Intzidis[4], K. Potska[5], C. Dogka[5], A. Katseli[5], D. Paranou[5], A. Karavaggeli[5], A.Meintani[5], D. Bouzarelou[5], **D. Lachanas**[5], G. Rigas[6], M. Kanara[7], M. Müslümanoglu[8], I. Bobolaki[9], E. Biziota[10], E. Papadopoulou[5], G. Nasioulas[5];[1]Medical School, University of Patras, Patras, GREECE, [2]3rd Dpt of Oncology, Interbalcan European Medical Centre, Thessaloniki, GREECE, [3]Oncology unit,Bioclinic, Thessaloniki, GREECE, [4]Breast Surgical Oncology Clinic, Theageneio Anticancer Hospital, Thessaloniki, GREECE, [5]Molecular Oncology, GenekorMedical SA, Attica, GREECE, [6]Breast Clinic, Agios Savvas Cancer Hospital, Attica, GREECE, [7]Breast Clinic, General Hospital of Trikala, Trikala, GREECE, [8]BreastClinic, Istanbul University School of Medicine, Instabul, TURKEY, [9]Oncology Department, General Hospital of Chania, Crete, GREECE, [10]OncologyDepartment,, Universal Hospital of Alexandroupoli, Alexandroupoli, GREECE.

Abstract

Background: Neurofibromatosis type 1 (NF1), is a classic example of a complete penetrance disease with an estimated prevalence of 1 in 3000. Broader application of multigene panel testing in candidate hereditary cancer predisposition cases, reveals pathogenic NF1 variants in Breast/ovarian/colorectal cancer patients without a clinical NF1 diagnosis. The scope of this study is to enlighten the contribution of NF1 to cancer risk in general population and the need of medical management guidelines in NF1 breast/ ovarian cancer patients lacking the relevant clinical phenotype.

Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder caused by pathogenic variants in the ***NF1*** gene. While individuals with NF1 typically present with recognizable clinical features—such as café-au-lait macules, neurofibromas, and Lisch nodules—recent advances in large-scale germline testing have revealed that NF1 variants may appear in patients lacking these classic signs. This emerging evidence suggests that NF1 pathogenic variants may be underdiagnosed in the broader cancer population.

The *NF1* gene functions as a tumor suppressor through negative regulation of the RAS/MAPK pathway. Germline *NF1* variants are associated with increased risks for multiple tumors, including breast cancer, malignant peripheral nerve sheath tumors, gliomas, and others. As multigene panel testing becomes more widely utilized in oncology care, identifying pathogenic *NF1* variants in patients without traditional NF1 features has become increasingly common—raising important questions about cancer risk, surveillance strategies, and diagnostic criteria.

Methods and Materials

This retrospective observational study included patients with mutated germline *NF1,* referred at GENEKOR Medical SA, Athens, Greece between the period of 1st Jan 2020 to 31st Oct 2024. High risk cancer patients, with no neural crest derivant malignancies, underwent germline mutation testing, with a 52 gene panel. All the *NF1* mutations were crosschecked via the ClinVar mutation database to be classified as pathogenic.

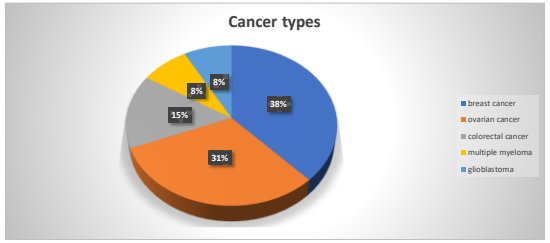

Figure 1. Cancer types as reason of referral

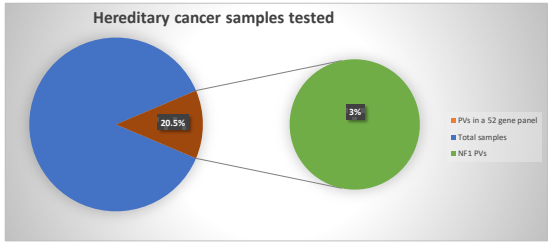

Figure 2. NF1 pathogenic variants among 12.782 cancer patients tested

Results

This retrospective observational study included 15 patients with incidentally identified mutated germline NF1, who were referred due to breast cancer (5/15, 33%), ovarian cancer (4/15,27 %), colorectal cancer (2/15,13%), multiple myeloma (1/15,7%) and glioblastoma (1/15,7%). Among the 12782 cancer patients, with no neural crest derivant malignancies,who underwent germline high-risk cancer gene susceptibility testing, 2616 (20.5%) cases had pathogenic mutations and 15 out of them (0.6%) were NF1 mutated. We identified an unexpectedly high prevalence (1 out of 852), of PVs in the NF1 gene, more than 3 times the rate expected given the reported prevalence of NF1. We identified 13 pLOF variants, 1 missense, 1 single amino acid deletion and 1 deletion involving the entire NF1 gene, all in heterozygosity, with the exception of 2 samples with blood mosaicism.

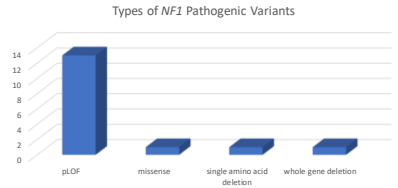

Chart 1. Types of pathogenic variants

Physical exam, medical and family history revealed no features consistent with NF1 diagnosis contrary to the complete penetrance of the disease. In 3 samples, additional PVs were identified, in *BRCA2* (ovarian cancer), *ATM* and *NTHL1* (2 colorectal cancer cases) genes.

Discussion

Our findings highlight a notably high prevalence of pathogenic NF1 variants among cancer patients who do not exhibit the classic clinical features of Neurofibromatosis type 1. This challenges the traditional assumption that NF1-associated tumor risk is confined primarily to individuals with recognizable NF1 phenotypes suggesting that NF1 may be an underappreciated contributor to cancer susceptibility in the general population. As multigene panel testing becomes routine in oncology, these variants are detected more frequently, revealing a broader phenotypic spectrum than historically recognized. Improved understanding of this population may refine clinical management and inform updated genetic testing guidelines.

.

Conclusions

This study investigates the prevalence and clinical significance of NF1 pathogenic variants in cancer patients who do not exhibit the classic phenotypic features of Neurofibromatosis type 1. Incomplete penetrance and missed diagnoses probably explain this. The aforementioned data presented provides insights into the need of establishment of screening and management strategies in patients with incidental findings.

Contact

GENEKOR S.A.
dlaxanas@genekor.com
www.genekor.com
0030-2106032138

References

Tsaousis G.N., Papadopoulou E, Apessos A, Agiannitopoulos K, Pepe G, Kambouri S, Diamantopoulos N, Floros T, Iosifidou R, Katopodi O, Koumarianou A, Markopoulos C, Papazisis K, Venizelos V, Xanthakis I, Xepapadakis G, Banu E, Eniu DT, Negru S, Stanculeanu DL, Ungureanu A, Ozmen V, Tansan S, Tekinel M, Yalcin S, Nasioulas G. (2019) **Analysis of hereditary cancer syndromes by using a panel of genes: Novel and multiple pathogenic mutations.** BMC Cancer. 2019 Jun 3;19(1):535.

Tsaousis GN, Tsoulos, E. Papadopoulou, K. Agiannitopoulos, G. Pepe, N. Diamantopoulos, T. Floros, R. Iosifidou, C. Markopoulos7 K. Papazisis, V. Venizelos, G. Xepapadakis, E. Banu, D.T. Eniu, D. Stanculeanu, A. Ungureanu, S. Tansan, M. Tekinel, S. Yalcin, G. Nasioulas. (2019) **Multigene panel testing results for hereditary breast cancer in 1325 individuals: implications for gene selection and considerations for guidelines.** In: ESMO 2019 Congress: Annals of Oncology (2019) 30 (suppl_5): v25-v54. 10.1093/annonc/mdz239

Landry JP et al. **Comparison of Cancer Prevalence in Patients With Neurofibromatosis Type 1 at an Academic Cancer Center vs in the General Population From 1985 to 2020.** JAMA Netw Open. 2021 Mar 1;4(3):e210945. doi: 10.1001/jamanetworkopen.2021.0945

. Wang X et al. **Breast cancer risk and germline genomic profiling of women with neurofibromatosis type 1 who developed breast cancer.** Genes Chromosomes Cancer. 2018 Jan;57(1):19-27. doi: 10.1002/gcc.22503