OPEN ACCESS

GAVIN PUBLISHERS

Journal of Oncology Research and Therapy

Brozek I, et al. J Oncol Res Ther: JONT-155.

DOI: 10.29011/2574-710X. 000055

Case Report

Ovarian Cancer in a Family with Coexistence of Germline *NF1* and *BRCA1* Mutations: Case Report

Izabela Brozek[1*], Magdalena Ratajska[1*], Magdalena Koczkowska[1], Alina Kuzniacka[1], Magdalena Krygier[1], Jaroslaw Debniak[2], Bartosz Wasag[1], Janusz Limon[1]

[1]Department of Biology and Medical Genetics, Medical University of Gdansk, Debinki 1, 80-211 Gdansk, Poland

[2]Department of Gynaecology, Gynaecological Oncology and Endocrinology, Medical University of Gdansk, Kliniczna 1a, 80-402 Gdansk, Poland

[*]**Corresponding authors:** Magdalena Ratajska, Department of Biology and Medical Genetics, Medical University of Gdansk, Debinki 1, 80-211 Gdansk, Poland. Tel: +48583491533; Fax: +48583491535; email: mratajska@gumed.edu.pl

Izabela Brozek, Department of Biology and Medical Genetics, Medical University of Gdansk, Debinki 1, 80-211 Gdansk, Poland. email: izabro@gumed.edu.pl

Citation: Brozek I, Ratajska M, Koczkowska M, Kuzniacka A, Krygier M, et al.(2018) Ovarian Cancer in a Family with Coexistence of Germline *NF1* and *BRCA1* Mutations: Case Report. J Oncol Res Ther: JONT-155. DOI: 10.29011/2574-710X. 000055

Received Date: 25April, 2018; **Accepted Date:** 14May, 2018; **Published Date:** 22May, 2018

Abstract

This report describes an individual affected by neurofibromatosis type 1 (*NF1*) and hereditary ovarian cancer, diagnosed with germline *NF1* and *BRCA1*mutations. The proband was a 37-year-old woman with symptoms typical for *NF1*, who developed ovarian adenocarcinoma serosum at 35 years of age. Another two malignant tumors, including carcinoma of the papilla of Vater and colorectal cancer were diagnosed in the proband's relatives. Molecular analysis revealed the presence of two germline mutations: c.181T>G in *BRCA1* and c.2082del in *NF1*genes in all affected family members. In the current report, we confirm a transmission without recombination of these two closely located genes. Double mutation-positive individuals with *BRCA1* and a second independent mutation in a cancer-associated gene should be very carefully screened for different types of cancer, not only breast and ovarian cancers.

Keywords: *BRCA1*; *NF1*; Ovarian Cancer; Mutation

Background

Neurofibromatosis type 1 (*NF1*, MIM: 162200) is a common dominantly inherited genetic disorder with the prevalence of approximately one in 2,000-3,000 individuals [1]. The disease is caused by loss-of-function mutations in the *NF1* gene (MIM: 613113), encoding a neurofibromin protein which is involved in cellular proliferation and tumor suppression [2]. The diagnosis of *NF1* is based on characteristic, but highly variable clinical findings, such as multiple café-au-lait spots (CALMs), axillary and inguinal skinfold freckling, cutaneousand /or subcutaneous neurofibromas, Lisch nodules as well as the presence of a first-degree relative meeting the NIH diagnostic criteria[3]. *NF1*-affected individuals have an increased risk of developing nervous system tumors, including optic pathway gliomas and malignant peripheral nerve sheath tumors. In addition, a higher incidence of various neoplasms has been described in patients with comparing to the general population[4]. It has been reported that women with *NF1* under 50 years of age have a fivefold increased risk of developing breast cancer and thus are considered to be in the moderate risk category[5]. However, limited data are available for the co-incidence of ovarian cancer in *NF1*-affected individuals. The penetrance for ovarian cancer among the cancer-predisposing germline mutations is the highest for mutations in the *BRCA1* gene (MIM: 113705), located near the *NF1* locus on chromosome 17. The concomitance of two independent *BRCA1* and *NF1* mutations in an individual is very rare and have been reported in only two families to date [6,7]. Here, we describe a patient with the coexistence of pathogenic *NF1* and *BRCA1* alterations, who developed clinical symptoms typical for NF1 and early-onset ovarian adenocarcinoma.

Case Presentation

Family Pedigree

On physical examination the 37-year-old proband (Figure 1;4-3) presented with multiple CALMs, axillary freckling and cutaneous neurofibromas. At 35 years of age she developed ovarian cancer, histologically described as a high grade adenocarcinoma serosum. The proband's younger sister (4-2) also fulfilled the NIH diagnostic criteria for *NF1* (multiple CALMs and cutaneous neurofibromas). The proband's father (3-3) and younger paternal half-sister (4-1) were both healthy. The proband's mother (3-5) was also affected with *NF1*, but no detailed information was available as she died at the age of 29 years due to carcinoma of the papilla of Vater. The individual's maternal aunt (3-6) was diagnosed with colorectal carcinoma at 60 years of age, while another two maternal aunts (3-7), three maternal uncles (3-8) and the maternal grandmother (2-3) were healthy. Furthermore, there was no family history of malignant tumors or *NF1* in the proband's paternal relatives.

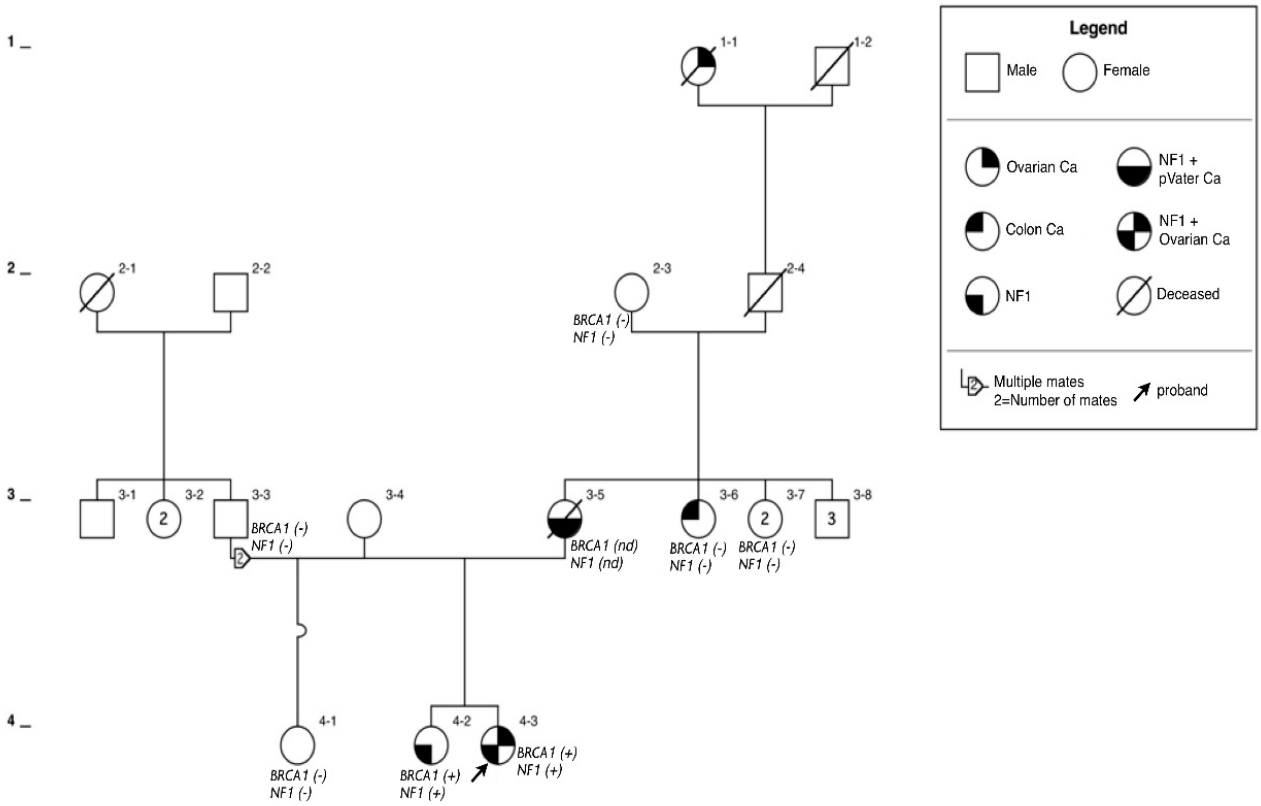

Figure 1: Pedigree of family diagnosed with mutations in *BRCA1* and *NF1*. (↗) - proband; (/) deceased; (-) wild-type individuals; (+)individuals carrying mutation; (nd) - not done.

Material and Methods

The proband's genomic DNA was extracted from the whole blood using the standard protocol with proteinase K digestion, phenol-chloroform extraction and ethanol precipitation. DNA was quantified using Qubit 2.0 Fluorometer. Molecular analysis was performed by using TruSight Cancer panel and MiSeq System according to the manufacturer's protocols (Illumina Inc.). The mean region coverage depth was 2631.5 times. The presence of pathogenic *NF1* and *BRCA1* alterations was confirmed by bidirectional sequencing (ABI PRISM 3130, Life Technologies). Consequently, family members were offered *BRCA1* and *NF1* testing for the known mutations. Genomic DNA of the family members(2-3, 3-3, 3-6, 3-7, 4-1, 4-2) was extracted from buccal swabs using Kappa Express Extract Kit (Kapa Biosystems Inc.). The mutational status of *BRCA1*and *NF1* mutations was analyzed using KAPA HiFiHotStart PCR Kit (Kapa Biosystems, Inc.)

followed by bidirectional sequencing. Primers sequences and PCR conditions are available on request.

Written informed consent was obtained from all individuals. The study was approved by the Ethical Committee of the Medical University of Gdansk, Poland (NKBBN/304/2014).

Molecular Results

Mutational analysis revealed the presence of a missense mutation in the BRCA1 exon 5 [c.181T>G, p.(Cys61Gly)] and a frameshift mutation in the *NF1* exon 18 [c.2082del, p.(Leu695Cysfs*53)] in the proband (4-3) and proband's younger sister (4-2). In the remaining five individuals (2-3, 3-3, 3-6, 3-7 and 4-1) neither BRCA1 nor *NF1* mutations were detected.

Discussion

In the current report, we describe an individual affected by *NF1* and hereditary ovarian cancer, heterozygous for germline *NF1* and BRCA1 mutations. The *NF1* mutation causes the premature termination of protein synthesis, while a missense variant in BRCA1 is known to disrupt the BRCA1-BARD1 interaction, which abolishes E3 ubiquitin ligase activity of BRCA1-BARD1[8].The frequency of BRCA1 and *NF1* alterations in the Polish population is estimated to be 1:400 and 1:3-5000, respectively[1,9], thus their coexistence in individual is very rare.

Both genes are located on chromosome 17q, with BRCA1 placed about 20cM from *NF1*, hence the recombination between them is unlikely, but not impossible [7]. In the family described by Ceccaroni et al. with a germline BRCA1 mutation and the *NF1* clinical diagnosis, a single family member may have received a recombinant chromosome 17, containing only the BRCA1 mutation [6]. In the present report, we confirm a transmission without recombination of both genes in all affected family members.

To date, coexistence of alterations in *BRCA1* and *NF1* has been confirmed only once in a patient diagnosed with *NF1* and early-onset breast cancer [7]. Previously, a concomitant presentation of *NF1* and *BRCA1*-related tumors, including breast, ovarian and colon cancers, was described by Ceccaroni et al.[6], but the *NF1* diagnosis in the family was not molecularly confirmed, based only on the clinical criteria. Notably, the analysis of chromosome 17 DNA markers was compatible with the co-segregation of the same *NF1* and *BRCA1* alleles in all affected individuals. Breast, ovarian and serous peritoneal carcinomas diagnosed in this family could be explained by the presence of a pathogenic *BRCA1* mutation as they usually occurred in the *BRCA1*-positive family members. However, the origin and pathogenesis of a rectal cancer, diagnosed in a 27-year-old male with both a *BRCA1* alteration and *NF1* diagnosis was unclear. In this report, the occurrence of a gastrointestinal cancerin a single family memberwas also observed. Carcinoma of the papilla of Vater, a rare cancer accounting for only 0.2% of all gastrointestinal cancers with an onset usually above 60, was diagnosed in the proband's mother at the age of 29 years. Even though this type of cancer is neither in the spectrum of *BRCA1* nor *NF1*-related syndromes, an early age of presentation may suggest rather genetic than sporadic etiology. The question arises whether the co-existence of the two independent mutations in the same individual could influence development of this rare cancer. Importantly, it cannot be excluded that ampullary tumor was in fact a misdiagnosed carcinoid tumor, especially since the concomitant existence of an ampullary carcinoid tumor and neurofibromatosis was previously described [10]. Moreover, as many as 25% of all carcinoids of the ampulla of Vater are diagnosed in patients with *NF1*[11].

It is well documented that loss-of-function mutations in the *NF1* gene may predispose to a variety of benign and malignant tumors [4]. The most frequent *NF1*-related neoplasms include: peripheral nerve sheath tumors, gastrointestinal stromal tumors, rhabdomyosarcomas, carcinoid tumors, pheochromocytomas, optic pathway gliomas and othergliomas and leukemias[4,12]. Some studies have also shown an elevated risk of breast cancer in women with *NF1* (SIR=3.5), but specific explanation of this association is not enough investigated[13]. In contrast to breast cancer, *NF1* alterations have not been previously associated with the ovarian cancer susceptibility[5,13]. To date, only a few published studies have raised the possible role of the *NF1* gene in the pathogenesis of this type of cancer. In a large-scale analysis of the germline-somatic landscape of ovarian cancer, germline mutations in the *NF1* gene were identified in 8/429 cases[14]. Another study revealed a high frequency of neurofibromin 1 defects in ovarian serous carcinomas, manifesting in a markedly reduced or absent expression of *NF1* protein[15]. Additionally, Iyengar et al. described a significant decrease in *NF1* Type II isoform expression and an increase in Type I expression in the ovarian cancer cells[16].

Conclusions

In summary, we conclude that an early-onset ovarian cancer diagnosed in the proband could be explained by the presence of a pathogenic germline *BRCA1* mutation, however, an additional role of the *NF1* alteration in the pathogenesis of this neoplasm cannot be excluded. Especially since the risk of developing ovarian cancer in *BRCA1*-mutation carriers before 40 years is relatively low, estimated to be 0.28% per year between 35-39 years[17]. Therefore, with the coexistence of the *NF1* alteration, an ovarian cancer risk could be higher than in individuals with the *BRCA1*/2 mutations only. Malignant tumors in *NF1*-affected patients tend to occur at a younger age and they are usually associated with a poorer prognosis compared tosporadic tumors.

Moreover, the presence of non-malignant tumors may hamper the diagnosis of malignant changes in *NF1* patients.

Delay in cancer detection in patients with *NF1* could be a result of mistakenly identifying the malignant tumors as a manifestation of the basic medical condition.Considering the possible interaction between cancer-related pathways regulated by different genes, we postulate that individuals with the occurrence of a pathogenic *BRCA1*/2 mutation and an additional variant in a cancer-associated gene require careful screening for different types of cancer, not only breast and ovarian cancers.

Consent: Written informed consent for publication of this Case report was obtained from all the patients who were included in this study. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests: The author(s) declare that they have no competing interests.

Authors contribution: I.B. and M.Krygier examined all family members included in the study, collected medical information and drafted the manuscript; M.R. designed, carried out the molecular genetic studies (including NGS files alignment) and helped to prepare the manuscript; M.Koczkowska and A.K. collected material, extracted DNA and carried out the co-segregation studies, M.Koczkowska also helped to draft the manuscript; J.D. identified the patient and referred to genetic counseling; B.W. participated in the NGS experiments and helped to draft the manuscript; J.L. supervised the study and helped to draft the manuscript. All authors read and approved the final manuscript

Acknowledgements: The authors thank all the patients and their families for participating in this study.This study was supported by a Polish National Science Centre project: 2011/02/A/NZ2/00017 and by a statutory research program financed by the Polish Ministry of Science and Higher Education: 02-0002.

References

1. Uusitalo E, Leppävirta J, Koffert A, Suominen S, Vahtera J, et al. (2015) Incidence and mortality of neurofibromatosis: a total population study in Finland. J Invest Dermatol 135: 904-906.
2. Friedman JM (1998) Neurofibromatosis 1. 1998 Oct 2 In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018.
3. National Institutes of Health Consensus Development Conference (1988). Neurofibromatosis. Conference Statement. Arch Neurol. 45: 575-578.
4. Patil S, Chamberlain RS (2012) Neoplasms associated with germline and somatic *NF1* gene mutations. Oncologist 17: 101-116.
5. Sharif S, Moran A, Huson SM, Iddenden R, Shenton A, et al. (2007) Women with neurofibromatosis 1 are at a moderately increased risk of developing breast cancer and should be considered for early screening. Journal of medical genetics 44: 481-484.
6. Ceccaroni M, Genuardi M, Legge F, Lucci-Cordisco E, Carrara S, et al. (2002) *BRCA1*-related malignancies in a family presenting with von Recklinghausen's disease. Gynecologic oncology 86: 375-378.
7. Campos B, Balmana J, Gardenyes J, Valenzuela I, Abad O, et al. (2013) Germline mutations in *NF1* and *BRCA1* in a family with neurofibromatosis type 1 and early-onset breast cancer. Breast cancer research and treatment 139: 597-602.
8. Irminger-Finger I, Ratajska M, and Pilyugin M. (2016). New concepts on BARD1: Regulator of BRCA pathways and beyond. The international journal of biochemistry & cell biology 72: 1-17.
9. Brozek I, Cybulska C, Ratajska M, Piatkowska M, Kluska A, et al. (2011) Prevalence of the most frequent *BRCA1* mutations in Polish population. Journal of applied genetics 52: 325-330.
10. Hatzitheoklitos E, Buchler MW, Friess H, Poch B, Ebert M, et al. (1994) Carcinoid of the ampulla of Vater. Clinical characteristics and morphologic features. Cancer 73: 1580-1588.
11. Hartel M, Wente MN, Sido B, Friess H, Buchler MW (2005) Carcinoid of the ampulla of Vater. Journal of gastroenterology and hepatology 20: 676-681.
12. Ratner N, Miller SJ (2015) A RASopathy gene commonly mutated in cancer: the neurofibromatosis type 1 tumour suppressor. Nature reviews Cancer 15: 290-301.
13. Howell SJ, Hockenhull K, Salih Z, Evans DG (2017) Increased risk of breast cancer in neurofibromatosis type 1: current insights. Breast Cancer 9: 531-536.
14. Kanchi KL, Johnson KJ, Lu C, McLellan MD, Leiserson MD, et al. (2014) Integrated analysis of germline and somatic variants in ovarian cancer. Nature communications 5: 3156.
15. Sangha N, Wu R, Kuick R, Powers S, Mu D, et al. (2008) Neurofibromin 1 (*NF1*) defects are common in human ovarian serous carcinomas and co-occur with TP53 mutations. Neoplasia 10: 1362-1372.
16. Iyengar TD, Ng S, Lau CC, Welch WR, Bell DA, et al. (1999) Differential expression of *NF1* type I and type II isoforms in sporadic borderline and invasive epithelial ovarian tumors. Oncogene 18: 257-262.
17. Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, et al. (2003) Average risks of breast and ovarian cancer associated with *BRCA1* or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. American journal of human genetics 72: 1117-1130.