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

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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, cutaneous and/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 cooccurrence 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 frameshif 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 carcinoma in a single family member was 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 coexistence 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 other gliomas 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 to sporadic 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.

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