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The Role of *BRCA1* and *BRCA2* Genes in the Appearance of Pediatric and Adolescent Disorders

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Abstract

The genes *BRCA1* and *BRCA2* appear crucial role in development of hereditary breast and ovarian cancer. Hundreds of different types of mutations have been identified in these genes. The high risk mutations inactivate a very important and foolproof DNA repair process, thus increasing considerably the risk of diseases development such as breast and ovarian cancer.

These genes seem to have a significant influence and participation in appearance of pediatric diseases other than breast and ovarian cancer being important molecules in DNA repair process and cell cycle progression. Therefore further exploration and evaluation of these genes in the appearance of pediatric diseases may enhance the importance of prenatal audit.

Keywords: *BRCA1*; *BRCA2*; Pediatric and adolescent disorders; Cell cycle control

Abbreviations: AML: Acute Myelogenic Leukemia; *BRCA1*: Breast Cancer Gene 1; *BRCA2*: Breast Cancer Gene 2; CNS: Central Nervous System; DSB: Double Strand Breaks; FA: Fanconi Anemia; FANCD: Fanconi Anemia Disease; HR: Homologous Recombination; NHL: Non-Hodgkin's Lymphomas; NTDS: Neural Tube Defects; RB: Retinoblastoma; SBMM: Spina Bifida Meningo Myelocele; WRN: Werner Syndrome; WT: Wilms Tumor

Introduction

The *BRCA1* and *BRCA2* genes have a crucial role in multiple organ systems. *BRCA1* and *BRCA2* are key molecules of cell cycle control and participate in development of several

pediatric diseases such as anemia Fanconi, spina bifida, meningomyelocele, tumors of CNS fetal origin, premature mortality and infantile epileptic encephalopathy. The appearance of heterozygosity in *BRCA1* or *BRCA2* genes predisposes to cancer in childhood (**Figure 1**). Therefore the identification of mutations of *BRCA1* and *BRCA2* in the general population and the availability of screening tests becomes important for early diagnosis and evaluation. The purpose of this review is to provide pediatric diseases related to mutations in *BRCA1* or *BRCA2* genes displaying the main role of these genes in several diseases except breast and ovarian cancer.

Literature Review

The involvement of the *BRCA2* gene in CNS tumors with fetal origin

Nowadays genetic analysis has been made to identify the *BRCA* genes mutations. These methods based on sequencing analysis of exonic and adjacent intronic regions of the *BRCA1* and *BRCA2* genes by quantitative procedures of polymerase chain reaction. The identified germline mutations such as 6174abIT and 886delGT of *BRCA2* gene were identified in children with CNS embryonic tumors and confirmed that every parent was a carrier of *BRCA2* mutations [1,2]. Mutations in *BRCA1* and *BRCA2* genes are prevalent in Ashkenazi Jewish populations [1,2]. In many cases, the presence of these tumors was directly related to Fanconi anemia even if in 17 studied families by Reid et al. the diagnosis of Fanconi anemia was absent. Mutations of genes *BRCA1* and *BRCA2* have already been determined in many types of tumors, such as Wilms tumors, brain tumors including medulloblastoma, multiple erythema, astrocytoma, acute myeloid leukemia and acute lymphoblastic leukemia. In these cases where identified 23 allelic mutations of the *BRCA2* gene. Among these twenty-one patients developed childhood cancer and 9 of them developed

brain tumors [2]. In assays of genetic material were shown that in five cases of analyzed brain tissues had the mutation 886delGT of *BRCA2* gene [2], while according to Alter et al. 27 published cases of *FANCD1* and mutants of gene *BRCA2* revealed correlation between the deletion 6174delGT of *BRCA2* and brain tumor development [3].

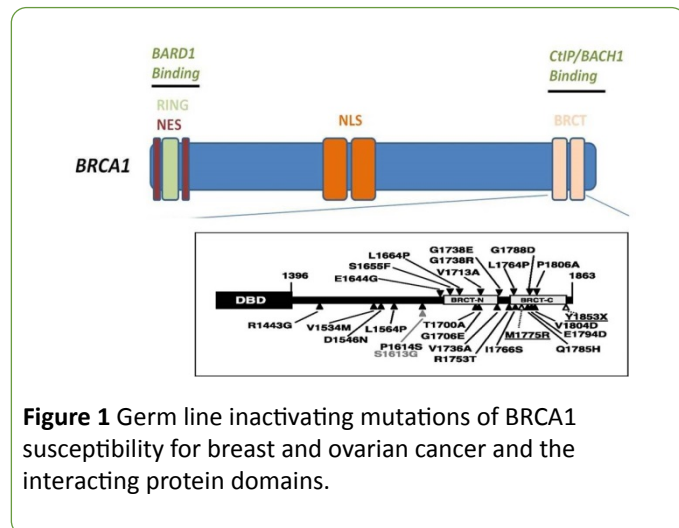


Figure 1 Germ line inactivating mutations of *BRCA1* susceptibility for breast and ovarian cancer and the interacting protein domains.

Identification of mutations of *BRCA1* gene in children with spina bifida and meningomyelocele (NTD)

The neural tube defects (NTDs) include a major group of genetic disorders with a total incidence of about 1-2 individuals per 1000 live births in the United States [4]. While NTD which characterized by loss of closure of the neural tube in the head is fatal, the appearance of spina bifida in the spinal cord area (spina bifida meningomyelocele) could be treated successfully. Spina bifida (meningomyelocele) (SBMM) is an important clinical entity that is caused by the limited closure of the spinal canal [5,6]. In mice deficient for *BRCA1* gene 40% of the embryos are presented with spina bifida and anencephaly [6]. Moreover, in embryos deficient for *BRCA1* gene the differentiation of neural tube is disorganized while people are characterized by increased risk of cell death [6].

A recent study by Wang et al. showed that the interaction between *BRCA1* and Gadd45a is essential for normal embryonic development in mouse models and the deregulation of the *BRCA1* gene by lack of exon 11 can induce apoptosis in mouse embryos [7]. In mouse models, the expression of the *BRCA1* (Bard1) is higher in the crust compared to the cerebellum and hippocampus [8]. In a mouse model with a deficit of exon 10 of *Brca1* the 40% of fetuses detected with exencephaly with disorganized neuroepithelium even if the spina bifida was normal in mice with *BRCA1* mutations [6,8]. According to Terri et al. two microsatellite regions are associated with the low number of repetitions of genes D17S1323 and D17S1322 at CEPH cells and the *BRCA1* gene is associated with the occurrence of spina bifida suggesting that *BRCA1* gene is essential for neuronal development [9].

The involvement of *BRCA1* gene in patients with premature mortality

According to the literature mutations of *BRCA1* gene have already determined in a neonate with fatal neonatal rigidity and multifocal seizure syndrome. Neonates with such gene mutations have hypertension, persistent seizures, frequent episodes of apnea, microcephaly, stagnation in the development of the head, lack of any development progress [10,11] and most patients survived until 21 months. DNA sequencing analysis data identified heterozygous variations in *BRCA1* gene. The exact role of *BRCA1* has not yet clarified, but there are evidences from *in vitro* studies in which the reading frame is affected. This results revealed differential interaction of the cell-cycle proteins [*BRCA1* and *ATM*] [8,12], disruption of the intracellular localization Drikos et al. [13] and possibly alterations in mitochondrial function [8].

BRCA1 and infantile epileptic encephalopathy

The *BRCA1* gene is mutated in a neonatal with fatal infantile epileptic encephalopathy. Recently described three cases of infants with persistent myoclonic seizures, hypertension and convulsions, poor growth of the head, inability to swallow, periods of apnea and bradycardia which led to cardiac arrest and death. In all cases, identified a mutation in the *BRCA1* gene (*BRCA1*). In addition the study of Hanes et al. presented two homozygotes with mutation of *BRCA1* gene [14]. In 2012, the Puffenberger et al. described a case of convulsion which started from the mold, small head circumference at birth, axial stiffness, rigidity of limbs, minor language disabilities and lack of developmental progress. Also noted frequent manifestations of spontaneous apnea and bradycardia leading to cardiopulmonary dysfunction. Subjects identified a novel homozygous mutation of c.638_639insA of *BRCA1* gene associated with severe corticobasal decomposition [15,16]. Therefore speculated that the instability and dysfunction of *BRCA1* protein is responsible for the occurrence of catastrophic epilepsy and neuronal atrophy [15,16]. Additionally two pups from Japan revealed progressive cerebral degeneration atrophy of the cerebellum and delayed myelination of white brain tissue [15,16].

Mutations in the genes *BRCA1* and *BRCA2* and their correlation with the occurrence of retinoblastoma

Genetic analysis of the *BRCA1* correlates this gene with methylation procedures of luminal tumors. The genomic instability is therefore common in cells that are characterized by mutations in *BRCA1* and *BRCA2*. Recently it has been shown that the tumor suppressor *PTEN* gene is disrupted by the *BRCA1* gene rearrangements [17]. FISH techniques in the *BRCA1* gene revealed rearrangements in cancer cells resulting in disruption of gene function and appearance of retinoblastoma [18]. An interesting observation is also recorded according to high frequencies of breakages of *RB1* gene especially in cancer subtypes with mutations of *BRCA1* gene and cells with methylation of *BRCA1*, indicating that the

BRCA1 and its structural changes affects tumor progression [19]. The genetic association of *BRCA1* and *RB1* genes is further supported by the identification of the physical interaction [20]. Thus, the highly proliferative capacity of basal breast carcinomas with mutated *BRCA1* cells could potentially be due to the interaction of *BRCA1* and *RB1*. The presence of chromosomal deficits of *RB1* genes are associated with the mutated forms of the *BRCA1* and significantly determines reduced expression of pRB to those cell types [19,20].

Additionally intracellular pathway of *RB1/E2F* regulates the expression of FA genes [21]. In patients suffering by *MYCN* and retinoblastoma, without affecting the path *RB1/E2F*, the *FANCA* gene is downregulated in comparison to patients who have not disturbed intracellular pathway of *RB1/E2F* [5,22]. The hyperactivity of the FA/*BRCA* pathway associated with increased resistance to certain drugs whereas suppression of FA/*BRCA* associated with increased susceptibility [2,23].

The association of *BRCA1* gene mutations in appearance Werner syndrome

The *BRCA1* protein interacts directly with the helicase *WRN* which appears exonuclease activity and the interaction between *WRN* and *BRCA1* increases in cell types which exposed to DNA mutagens. The treatment of DNA mutations *in vivo* in ICLs required the action of *WRN* as helicase but not as exonuclease. These observations suggest that the proteins *WRN* and *BRCA1* are involved in DNA repair in cases of ICLs. The ICLs form a covalent attachment between the two strands of the DNA helix [24]. These interactions of *WRN* and *BRCA1* during formation of DSBs in S phase may prevent the incorrect homologous recombination [HR] [25,26]. The absence of expression and activity of *BRCA1* or *WRN* genes induce increased frequency of DSBs during phase S such as *WRN* being located in the region *gH2AX* foci as studied by Lan et al. The *BRCA1* therefore support the helicase activity of the *WRN* as *BRCA1* and *WRN* interact in repair DNA processes. In Holliday repair process formed in fork structure *WRN* is determined [25-27]. The *BRCA1* support the function of *WRN* is fork structures [28].

Mutations of *BRCA* genes in patients with Wilms tumor

The Wilms tumor (WT) is a tumor with embryonic origin of the kidney which appears at 1 in 10,000 children. The incidence is determined in 1-3% of cases of childhood cancer and associated with mutations in *WT1* and *WT2* genes that have been mapped to chromosome 17q21 and 19q13.1-3. However, a significant percentage of cases the WT tumors appear to be related to these genetic regions [29]. Until recently there were restricted data correlate childhood cancers, such as WT with mutations in *BRCA1* and *BRCA2* genes. Patients who have undergone during childhood in chemotherapy and radiation approaches are more likely to spill malignancies such as cancer [30]. Henderson et al. reported an increased risk of secondary cancer during

childhood in patients with bone sarcomas, renal tumors, Hodgkin's lymphoma and WT [31].

Cotton et al. determined that 17% of patients with tumors of childhood die after the appearance of secondary neoplasm defined as late effects of treatment [32]. Furthermore Henderson et al. identified an 11-fold increased risk of secondary cancer in patients receiving treatment with radiation, especially breast cancer probably because of mutations in *BRCA1* and *BRCA2* [31,32]. According to this we can say that breast cancer is a common secondary cancer in surviving patients with Wilms tumor (WT) [33].

Additionally Robison reported a significant association of breast cancer in patients with WT [34]. Cheng et al. identified 29 cases of invasive breast cancer among survivors with WT and 4 cases occurred before the age of 40 [35]. Apart from treatment procedure of irradiation genetic factors may also affect tumor incidence of breast cancer in survivors of WT such as familial mutation in the *BRCA1* [36] or overexpression of *IGF2* gene [37].

Fanconi anemia and mutations in *BRCA1* and 2 genes

Fanconi anemia is a prime disease of pediatric age which has been associated with mutations in *BRCA1* and *BRCA2* genes. Fanconi anemia (FA) is transmitted as an autosomal recessive inheritance disease with direct linkage on chromosome X characterized by multiple congenital defects, failure of bone marrow and increased risk of cancer. *De novo* mutations of the *BRCA1* gene is closely associated with the occurrence of Acute myelogenous leukemia (AML) such as 32% of primary AML tumors and 75% of secondary AML tumors characterized by reduced expression of the *BRCA1* gene [38]. Alongside *BRCA2* mutations detected also in cases of non-Hodgkin's lymphomas (NHL) [38]. The protein products of the *BRCA1* and *BRCA2* genes interact with the protein of Fanconi anemia forming a powerful functional complex.

Discussion

The complex is capable of directing the Fanconi protein within the region of repair process. Mutations in the *BRCA2* gene (*FANCD1*) may appear in early childhood [39]. Some epidemiological studies have shown an increased risk of leukemia/lymphoma, in patients with specific mutations in the genes *BRCA1* or *BRCA2* [40]. The proteins *BRCA1*, *BRCA2* and Fanconi regulate the integrity of the human genome and operated via the FA/*BRCA*- pathway to repair DNA DSBs. The FA/*BRCA* pathway activated by the monoubiquitination of *FANCD2* and *FANCI*, which is considered to be crucial for the activation procedure. The FA pathway has also been shown to be upregulated in infection such as HPV - infection [41] and *BRCA1* appears to be localized to the cellular component of the centrosome.

According to this *FANCA* and *BRCA1*, interact with the transcription factor *E2F3* and appears to affect the function of the centrosome [42]. In agreement with studies of uterine

cancers revealed restricted expression of FANCA and *BRCA1* genes [43] and these tumors exhibit dysfunction of centrosome [44]. The FANCD2-Ub can interact with PCNA proliferating cell nuclear antigen [34,44] and *BRCA2/RAD51* functionally interacts with FANCD2 complex [45,46]. The *BRCA2/RAD51* complex is not sufficient to promote the process of homologous recombination in the absence of the FANCD2-Ub and especially to localize complex into the nucleus after HU exposure [47]. Furthermore mutations may cause destabilization of *BRCA2/FANCD1* complex influence homologous recombination demonstrating a nonfunctional complex in DSB sites.

Conclusion

BRCA1 and *BRCA2*, appear a very important role in DNA repair, homologous recombination and transcription. If there is damage to important control molecules of cell cycle, such as p53, RAD51, *BRCA1* and *BRCA2* disrupt proliferation and carcinogenesis. *BRCA1* and *BRCA2* apart from carcinogenesis seem to have a decisive role in the emergence of many pediatric diseases making prenatal screening important in determining the potential risk of such pediatric disorders.

Authors' Contributions

Ioannis Drikos, Alexandros Sachinidis, Ioanna Vassi, Effrossyni Boutou participated in the design of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interests

The authors declare that they have no competing interests.

Ethical Approval

This article does not contain any studies with human participants performed by any of the authors.

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