Variation in the BRCA2 gene in a child with medulloblastoma and a family history of breast cancer

Case report

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The fact that BRCA genes operate as tumor suppressors is evident from the genetics of the different human disorders caused by inherited mutations. Germline mutations affecting 1 allele of either BRCA1 or BRCA2 confer susceptibility to different types of cancers such as breast cancer and medulloblastoma. A family with a history of cancer was identified in Eastern Turkey in which one of the family members (a 13-year-old boy) had medulloblastoma. Venous blood was collected from available family members. The BRCA1 and BRCA2 genes were sequenced in the patient with medulloblastoma and the healthy father. An Asn372His homozygous variation was noted in the BRCA2 gene in the patient with medulloblastoma whereas the variation was heterozygous in the healthy father. A biallelic homozygous variation was demonstrated in the BRCA2 gene, which is important in medulloblastoma suppression, and may have caused medulloblastoma formation in the 13-year-old boy. Further investigations in large human populations with medulloblastoma are necessary for further delineation of BRCA gene malfunctions and their relationship to medulloblastoma formation, and to clarify the therapeutic implications of these malfunctions.

DOI: 10.3171/2011.8.PEDS11210

Key Words • medulloblastoma • BRCA1 • BRCA2 • breast cancer • oncology
Homozygous change in the BRCA2 gene in medulloblastoma

Case Report

This 13-year-old boy presented to our emergency service with a sudden onset history of headache, nausea, vomiting, balance disorder, and confusion. His cranial CT scan revealed a posterior fossa mass, and the patient was thus hospitalized. On cranial MR imaging, the lesion showed heterogeneous enhancement (Fig. 1A–C). Radiological diagnosis was a primitive neuroectodermal tumor, possibly medulloblastoma. The patient underwent a posterior fossa craniotomy and gross-total tumor excision. The postoperative period was uneventful. The preoperative diagnosis was corrected to desmoplastic medulloblastoma after histopathological examination of the tumor (Fig. 1D and E).

In recording the family medical history of the patient, we learned that the patient’s mother and her 3 sisters had died of early onset breast cancer, and the brother of the patient’s mother had died from liver cancer (Fig. 2A). Mutational analysis of the BRCA1 and BRCA2 genes demonstrated a homozygous AAT to CAT (Asn372His) change in exon 5 of the BRCA2 gene in the 13-year-old boy, which was heterozygous in the father (Fig. 2B). This variant is known to be associated with breast cancer risk.5

Discussion

A significant hazardous DNA lesion on the cell is a double-strand break.4 Homologous recombination is one of the biochemical repair pathways and plays a dual role in eukaryotic organisms. First, it is responsible for the creation of genetic variability during meiosis by directing the formation of reciprocal crossovers that then result in random combinations of alleles and traits. Secondly, in mitotic cells, the homologous recombination maintains the integrity of the genome by promoting the faithful repair of DNA double-strand breaks.4,9 In vertebrates, this homologous recombination therefore plays a key role in tumor avoidance. Mutations of the tumor suppressor protein BRCA2 are associated with a predisposition to different cancer types, and loss of BRCA2 function leads to genetic instability.4,9 The BRCA2 protein interacts directly with the RAD51 recombinase and regulates recombination-mediated double-strand break repair, accounting for the high levels of spontaneous chromosomal aberrations seen in BRCA2-defective cells. The BRCA2 tumor suppressor is a universal regulator of recombinase actions.9 The essential role of BRCA genes in preserving the integrity of chromosome structure indicates that their inactivation may work indirectly to initiate or promote carcinogenesis. Tumor-suppressor genes of this type are known as “caretakers.” By triggering genomic instability, their inactivation is believed to increase the likelihood of mutation or an altered expression of “gatekeeper” genes, which control cell division, death, and lifespan, thus promoting the outgrowth of cancer cells.10

Biallelic point mutations of BRCA2 cause solid tumors of different organs, including medulloblastoma.1,5–7 Frappart et al.3 determined the role of BRCA2 in medulloblastoma development by inactivating murine BRCA2 throughout the neural tissues. They found that BRCA2 loss profoundly affects neurogenesis. They also reported that when they inactivated BRCA2 in mice, rapid formation of medulloblastoma was observed with extensive

Fig. 1. A–C: Cranial axial (A), coronal (B), and sagittal (C) MR images show an enhancing mass in the posterior fossa. The photomicrographs (D and E) show desmoplastic medulloblastoma cells with a high mitotic index. H & E, original magnification × 40 (D), × 100 (E).
II-1 had liver cancer. II-4, and II-5 all died of early onset breast cancer, and family member indicates the index case (13-year-old boy). Family members II-2, II-3, II-6 had breast cancer, and II-3 had prostate cancer.

Because the BRCA proteins do have a central role in the repair of double-strand breaks, this feature may offer possible approaches to therapy for medulloblastoma. Agents that arrest replication, such as platinum compounds, and agents that exploit the inability of homologous recombination-deficient cancer cells to cope with stalled DNA replication forks, such as inhibitors of the enzyme poly-ADP-ribose polymerase I (which blocks the DNA repair pathway), are examples. These kinds of agents are currently under investigation for the treatment of different cancer types, including medulloblastoma.

In our study, we analyzed the BRCA2 gene in a family with a history of cancer whose members have experienced early onset breast cancer, liver cancer, and medulloblastoma. The amino acid change was from asparagine to histidine (Asn372His), which is reported as a polymorphism in different populations. This polymorphism is associated with breast cancer risk. A medulloblastoma was diagnosed in a young child with an embryonal CNS tumor. The amino acid change in the BRCA2 gene was homozygous in the index case (the patient) and heterozygous in the healthy father.

Fig. 2. A: Pedigree of the family with a history of cancer. Arrow indicates the index case (13-year-old boy). Family members II-2, II-3, II-4, and II-5 all died of early onset breast cancer, and family member II-1 had liver cancer. B: Chromatogram of the variation in the BRCA2 gene.

cH2AX. Their data illustrate the importance of BRCA2 during CNS development and that it is required to suppress medulloblastoma formation.

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In our study, we analyzed the BRCA2 gene in a family with a history of cancer whose members have experienced early onset breast cancer, liver cancer, and medulloblastoma. The amino acid change was from asparagine to histidine (Asn372His), which is reported as being associated with breast cancer risk. A medulloblastoma carrier (the index case) was in a homozygous state for this change while the healthy father was in a heterozygous state. In our patient, this variation in the BRCA2 gene possibly caused instability in the structures of the chromosomes and also a loss of tumor suppressor function for the BRCA2 gene and a state of inactivation for the BRCA2 function with the existing variation resulting in increased mutation or altered expression of the genes that control cell division and lead to medulloblastoma formation. Further investigations of BRCA2 genomic alterations and functions in large patient populations with medulloblastoma can provide additional information to what we currently know about the molecular pathogenesis of medulloblastoma and may pave the way for future positive development in the treatment of this cancer.

Disclosure

This work was supported by the Scientific Research Project Fund of Cumhuriyet University (no. T-435). Author contributions to the study and manuscript preparation include the following. Conception and design: Bayrakli, Soylemez, Kaplan, Gurelik. Acquisition of data: Bayrakli, Akgun, Soylemez, Gurelik. Analysis and interpretation of data: Bayrakli. Drafting the article: Bayrakli, Akgun, Soylemez, Kaplan. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Bayrakli.

References


Manuscript submitted May 21, 2011. Accepted August 4, 2011.

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