# Medulloblastoma Etiology

The exact cause (etiology) of medulloblastoma is not fully understood, but several factors and genetic alterations have been implicated in its development. Here are some key factors associated with the etiology of medulloblastoma:

Genetic Predisposition: Some individuals may have a genetic predisposition to developing medulloblastoma. Mutations or alterations in specific genes, such as PTCH1 (associated with Gorlin syndrome) or TP53, have been linked to an increased risk of medulloblastoma. Gorlin syndrome, in particular, is a hereditary condition that increases the risk of developing medulloblastoma and other cancers.

Sporadic Mutations: In many cases, medulloblastoma occurs sporadically without a clear genetic predisposition. Sporadic mutations in critical genes or pathways may contribute to tumor development. For instance, mutations in the WNT, SHH, and Group 3/4 subgroups of medulloblastoma have been identified as important drivers of the disease.

Radiation Exposure: Exposure to ionizing radiation, particularly during early childhood, is a well-established risk factor for medulloblastoma. This is most commonly associated with therapeutic radiation for other medical conditions, such as radiation therapy for a different type of cancer. Radiation exposure can damage DNA and increase the risk of cancer, including medulloblastoma.

Sonic Hedgehog (SHH) Signaling Pathway: Dysregulation of the SHH signaling pathway has been implicated in the medulloblastoma pathogenesis. Mutations in genes within this pathway, such as PTCH1 or SMO, can lead to the uncontrolled growth of cells in the cerebellum, where medulloblastomas often develop.

WNT Signaling Pathway: Abnormal activation of the WNT signaling pathway, often due to genetic mutations, is associated with a subset of medulloblastomas. This pathway plays a role in the regulation of cell growth and differentiation.

Group 3 and Group 4 Subtypes: These are two subtypes of medulloblastoma that lack well-defined genetic mutations but are often characterized by complex genetic alterations. These subtypes are more common in older children and adults.

It's important to note that medulloblastoma is a heterogeneous disease, meaning that different subgroups of medulloblastoma may have distinct genetic alterations and clinical characteristics. Researchers are continually studying the genetic and molecular underpinnings of medulloblastoma to better understand its etiology and develop targeted therapies.

While certain risk factors and genetic mutations have been identified, most cases of medulloblastoma occur sporadically without a clear predisposing factor. Early diagnosis and a combination of surgical resection, radiation therapy, and chemotherapy are often used in the treatment of medulloblastoma, and the choice of treatment depends on the age of the patient, the tumor subtype, and the extent of the disease.

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Li et al. compared the gene expression levels in the four different medulloblastoma groups (MB-WNT, MB-SHH, MB-G3, and MB-G4), with a focus on genes associated with mitochondria. They used several

tools including Salmon, Tximeta, DESeq2, BiomaRt, STRING, Ggplot2, EnhancedVolcano, Venny 2.1, and Metscape.

A total of 668 genes were differentially expressed and the most abundant genes were associated with the cell division pathway followed by modulation of chemical synaptic transmission. We also identified several genes (ABAT, SOX9, ALDH5A, FOXM1, ABL1, NHLH1, NEUROD1 and NEUROD2) known to play vital role in medulloblastoma. Comparative expression analysis revealed OXPHOS complex-associated proteins of mitochondria. The most significantly expressed genes in the MB-SHH and MB-G4 groups were AHCYL1 and SFXN5 while PAICS was significantly upregulated in the MB-WNT group. Notably, MB-G3 contained the most downregulated genes from the OXPHOS complexes, except COX6B2 which was strongly upregulated. They show the importance of mitochondria and compare their role in the four different medulloblastoma groups [1)].

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Several lines of evidence implicate granule neuron precursors (GNP) in the external granule layer (EGL) of the developing cerebellum as likely cells of origin for certain classes of medulloblastomas.

1). For example, cells that compose a preneoplastic stage of medulloblastoma colocalize with GNPs in the EGL and they express molecular markers of immature granule neurons ( 2). Another possible medulloblastoma cell of origin has been identified: a neural progenitor located in the cerebellar white matter and expressing both nestin and prominin ( 3). Signal transduction pathways that stimulate proliferation and inhibit differentiation of GNPs and other neural progenitor cells during development have been implicated in medulloblastoma. Thus, understanding the mitogenic functions of these pathways will yield insights into medulloblastoma formation.

The overexpression of proteins that normally stimulate the proliferation of neural progenitor cells may initiate medulloblastoma formation. Two known mitogens for neural progenitors are the c-Myc oncoprotein and Sonic hedgehog (Shh), a crucial determinant of embryonic pattern formation in the central nervous system.

Several genes have been implicated in the development of medulloblastoma in children, including Patched-1 and Smoothened. The protein products of these genes function within the sonic hedgehog molecular signaling pathways, which are important in neural development and disease.

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Li Q, Jia Y, Tang B, Yang H, Yang Q, Luo X, Pan Y. Mitochondrial subtype MB-G3 contains potential novel biomarkers and therapeutic targets associated with prognosis of medulloblastoma. Biomarkers. 2023 Oct 27:1-16. doi: 10.1080/1354750X.2023.2276670. Epub ahead of print. PMID: 37886818.