Genetics of choroid plexus tumors

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Choroid plexus tumors consist of papillomas and carcinomas. A variety of germline and somatic genetic changes have been demonstrated for each of these subtypes. In this paper, the authors summarize the current knowledge of the genetic bases of these tumors.

KEY WORDS • choroid plexus carcinoma • choroid plexus papilloma • *TP53* gene • *hSNF5/INI1* gene • genetics

Choroid plexus tumors are rare tumors of neuroectodermal origin. They represent approximately 0.5% of all brain tumors, and their annual incidence is 0.3 cases per 1 million population.^{5,29} Associated with the development of these tumors are both germline and somatic abnormalities located at several genetic loci.

The TP53 Gene

The *TP53* gene is located on 17p13.1; this gene expresses the protein product p53, which influences tumor suppression via a variety of mechanisms including DNA repair, apoptosis, cellular differentiation, and angiogenesis.¹⁸ A mutation of the *TP53* gene causes a loss of p53 function as well as prolongation of the half life of the protein. This means that increased immunohistochemical staining for p53 protein can be used as a surrogate marker of gene mutation.¹⁴

Choroid plexus carcinomas are one of the tumors found in Li-Fraumeni families with *TP53* germline mutations.^{8,10,26,27} In addition, spontaneous germline and somatic p53 mutations have both been identified in patients with choroid plexus carcinomas.^{28,32} Positive nuclear staining for p53 protein is evident in the majority of choroid plexus carcinomas (10 of 11), whereas it is only seen rarely in choroid plexus papillomas (one of 12).³ Mutations of *TP53* have not been extensively studied in patients with choroid plexus papillomas; however, germline mutations have been reported.^{11,16}

The hSNF5/INI1 Gene

The *hSNF5/INI1* gene is located on 22q11.2 and encodes a member of the SWI/SNF adenosine triphosphate-dependent chromatin-remodeling complex.¹⁷ Germline mutations of this gene have been described as rhabdoid predisposition

syndrome. In families with this mutation, researchers have identified the development of both renal and extrarenal malignant rhabdoid tumors, choroid plexus carcinomas, atypical teratoid rhabdoid tumors, and medulloblastomas.^{17,23} Somatic mutations of the *hSNF5/INI1* gene have also been reported in cases of choroid plexus carcinoma.³² Authors of several papers offer descriptions of the genotypic and phenotypic overlap between choroid plexus carcinomas and atypical teratoid rhabdoid tumors;^{4,30} however, immunohistochemical studies have shown that, in the majority of cases of choroid plexus carcinomas, *hSNF5/INI1* protein expression is preserved.^{6,7} It therefore has been suggested that tumors believed to be choroid plexus carcinomas with *hSNF5/INI1* mutations may actually be atypical teratoid rhabdoid tumors.⁶

There is no evidence of *hSNF5/INI1* point mutations in patients with choroid plexus papilloma.¹¹

Other Syndromes

Aicardi syndrome is a rare, X chromosome-linked dominant condition that is observed in female patients. When it does occur in males with the normal allotment of sex chromosomes, this condition proves lethal during the early gestational period.¹ Affected female patients have callosal agenesis, infantile seizures, and chorioretinal lacunae. These children have visual impairments and usually display severe developmental delays and problematic seizures. Several authors have reported choroid plexus papillomas in girls with Aicardi syndrome.^{1,22,24,25}

Hypomelanosis of Ito is a descriptive condition caused by a variety of chromosomal abnormalities and is often associated with other neurological and skeletal abnormalities. In the setting of an X;17(q12;p13) translocation, hypome-

lanosis of Ito has been associated with the development of choroid plexus papillomas.^{20,21,31}

The constitutional 9p duplication is another rare abnormality whose association with choroid plexus hyperplasia and choroid plexus papilloma has been reported.¹² Extra copies of chromosome arm 9p have also been found in patients harboring either a sporadic choroid plexus papilloma or carcinoma—a finding that implicates this locus in the formation of both of these tumors.¹⁵

Chromosomal Imbalances

Multiple chromosomal imbalances have been described in reports of comparative genomic hybridization of choroid plexus tumors.¹⁵ Patients with choroid plexus papillomas have frequently displayed the following chromosomal additions and deletions: +7q (65%); +5q (62%); +7p (59%); +5p (56%); +9p (50%); +9q (41%); +12p and +12q (38%); +8q (35%); -10q (56%); -10p, and -22q (47%). Patients with choroid plexus carcinomas have primarily displayed the following additions and deletions: +12p; +12q, and +20p (60%); +1, +4q, and +20q (53%); +4p (47%); +8q and +14q (40%); +7q, +9p, and +21 (33%); -22q (73%); -5q (40%); -5p and -18q (33%). Certain imbalances are characteristic of the type of tumor and the age of the patient at presentation; from this we can infer a different genetic basis for these tumor variations. A survival analysis showed a survival advantage in patients with choroid plexus carcinomas in whom there was a gain of 9p and a loss of 10q ($p = 0.0186$, log-rank test). Nevertheless, the population group in this analysis was small (10 patients) and was not controlled for different treatments.¹⁵

Polyomavirus Infection

The related ubiquitous polyomaviruses SV40, JC, and BK have been implicated in the development of choroid plexus neoplasms.^{2,9,10,13} Choroid plexus tumors are induced experimentally when the common viral gene product, T antigen, is transgenically expressed in mice.¹⁹ The mechanism of action is the binding of the large T antigen with both p53 and pRb tumor suppressor proteins, complexes demonstrated in humans harboring choroid plexus tumors.^{2,33}

Conclusions

A variety of genetic loci are implicated in the development of choroid plexus carcinomas and choroid plexus papillomas. The loci associated with carcinoma generally differ from those associated with papilloma, which leads us to infer a separate genetic basis for these two phenotypically related lesions. Carcinomas, in particular, can be difficult to manage in very young patients, and increased knowledge of the molecular biology of these tumors will hopefully lead to improvements in their treatments and outcomes.

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Genetics of choroid plexus tumors

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