

Cancer Prone Disease Section

Mini Review

Turcot syndrome

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Identity

Other names: Malignant tumors of the central nervous system associated with familial polyposis of the colon.

Note: Turcot syndrome (TS) is characterized by the association of colonic polyps and central nervous system tumors. The relative risk of cerebral tumor in patients with familial adenomatous polyposis is considered 92 times more than that found in the general population. The predominant brain tumors are medulloblastoma and gliomas.

Inheritance: Both autosomal dominant and autosomal recessive modes of inheritance have been described, based on the analysis of familial segregation of the disease and the results of molecular studies. Nevertheless, considering the low penetrance and rarity of TS, the involvement of a major gene in association with a second locus containing a modifier gene or of environmental factors has been suggested.

Clinics

Neoplastic risk

Cardinal findings in TS are colonic polyps with tendency to colorectal cancer and malignant central nervous system tumors.

Colonic polyps: Three types of polyposis coli are described to occur in TS: 1) Type 1 is characterized by multiple colonic polyps numbering between 20 and 100, some of which may exceed 3 cm in diameter; 2) Type 2 is characterized by a small number of colonic polyps, usually less than 10; 3) Type 3 is characterized by numerous small colonic polyps similar to those of classical familial polyposis coli. Based on molecular entities, two groups can be differentiated: the one due to mutation in the APC gene (see below), characterized by colonic polyps, the second one due to mutations in the DNA mismatch repair (MMR) genes (see below) and

characterized by colorectal adenomas without polyposis.

Colorectal cancer: the polyps frequently show malignant transformation in the second and third decades of life.

Central nervous system tumors: Two major types of TS are distinguished based on different types of central nervous system tumors. The first one is characterized by childhood cerebellar medulloblastoma and the second by gliomas, particularly glioblastoma multiforme, arising in both children and adult. The two different types are related to different molecular pathogenesis. In fact, the first type is caused by mutations in the APC gene (see below), whereas the second type is related to MMR genes mutations (see below).

Other: In some instances, patients with TS have additional symptoms characteristic of other genetic conditions with familial polyposis of the coli, including pigmented ocular fundus lesions, epidermal inclusion cysts, osteosclerotic jaw lesions, cafe-au-lait spots or lipomas.

Cytogenetics

Note: Chromosome analysis is generally normal in patients with TS

Genes involved and Proteins

APC (Adenomatous Polyposis of the Colon)

Location: 5q21

Note: The APC locus consists of 15 exons.

Protein

Function: APC: APC seems to be involved in cell adhesion with a role in the beta-catenin -APC interaction. It is possible that the APC complex

regulates transmission of the contact inhibition signal into the cells, since APC mutations are associated with the development of hyperplasia, an early event in tumorigenesis. Alternatively, it is possible that the APC-catenin complex regulates adhesions, since loss of cadherin-mediated adhesion can contribute to metastasis

Mutations

Germline APC mutations are detectable in 2/3 of patients with TS. In the remaining patients, germline mutations in MMR genes can be found. Molecular analysis have shown that heterozygous, homozygous or compound heterozygous mutations may be implicated in TS. TS caused by APC mutations is associated with childhood cerebellar medulloblastoma and colonic polyps, while TS related to MMR genes is associated with glioma and colorectal adenomas without polyposis. Nevertheless, there is a wide clinical heterogeneity among carriers of mutations in the same gene, and even among pedigrees segregating for the same molecular defect. Such variations could be accounted for by genetic or environmental modifiers.

MLH1

Location: 3p21.3

Note: The MLH1 locus encompasses approximately 100 kb and consists of 19 exons.

Protein

Function: MMR genes: MLH1 and PMS2 are involved in DNA mismatch repair, and neoplasms of affected patients show DNA replication errors.

PMS2

Location: 7p22

Note: The PMS2 locus encompasses 16 kb and consists of 15 exons

Mutations

PMS2 mutations have been identified in a few families so far, and a very severe phenotype has been described in most of the cases.

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