Attenuated familial adenomatous polyposis with desmoids caused by an APC mutation

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We present here a case of attenuated familial adenomatous polyposis (AFAP) with a family history of desmoids and thyroid tumors. This patient had no colonic polyps but did have multiple desmoids. Genetic analysis identified a 4-bp deletion in codon 2644 (c.7932_7935delTTAT: p.Tyr2645LysfsX14) of the adenomatous polyposis coli (APC) gene. In cases with limited numbers of colonic polyps and desmoids, AFAP may be caused by a mutation in the 3' region of APC.
screening by direct sequencing using the Sanger method, and no other variants were identified. Among the six variants, five were synonymous single nucleotide variants and one was a nonsynonymous single nucleotide variant (Table 1), as determined by evaluations using public databases, including dbSNP (in NCBI), the HapMap project and the Human Genetic Variation Browser. The remaining variant detected by whole-genome sequencing was a 4-bp deletion of nucleotides 7932 to 7935, c.7932_7935delTTAT: p.Tyr2645LysfsX14 (Table 1, Figure 1b), located outside of the region that we had initially screened. This variant causes a frame shift, leading to a premature stop codon near the 3′ end of APC. An identical mutation has been deposited in the International Society for Gastrointestinal Hereditary Tumours (InSiGHT) Variant Databases and has been reported on two different pedigrees. Although no detailed clinical information was supplied for one of the two patients with this mutation, the family history of the other showed that four of six affected family members developed desmoid tumors. The patient evaluated in this study also had a family history of desmoid tumors. Notably, the father and aunt in our case developed thyroid cancer, although histological data of their tumors are not available. These findings suggest that this mutation impairs the functioning of the APC product that is responsible for the suppression of desmoids and thyroid cancer.

The APC gene product possesses several domains that are critical for its function. The most prominent function of APC is its ability to regulate Wnt/β-catenin-mediated gene transcription. Mutations in the mutation cluster region lead to the loss of the ability to suppress β-catenin-mediated signaling, which plays a crucial role in the development of colorectal adenoma. The mutant APC protein identified in this study is assumed to have a domain that interacts with β-catenin, which may account for her lack of adenomatous polyps. Reportedly, other mutations located...
within the 3’ region of APC may also lead to the development of desmoid tumors.12,13 Interestingly, the accumulation of mutations at the 3’ end of APC.14 Thus, a second hit in the wild-type APC allele may suppress the function of the truncated APC protein containing the β-catenin-interacting domain. Because the mutation in this case leads to the truncation of approximately 200 C-terminal amino acids, the mutant protein likely lost domains for interacting with EB1 and human homolog of Drosophila discs large (hDLG).15,16 The APC-EB1 and APC-hDLG complexes are reportedly important for the regulation of chromosome segregation and the cell cycle, respectively.17,18 Therefore, the loss of interaction of this APC product with EB1 and hDLG might cause the deregulation of cell division and proliferation.

With regard to thyroid cancer in FAP, the genotype–phenotype correlation is controversial. Recently, Septer et al.19 have reported an increased risk of thyroid cancer in FAP patients with a mutation at the 5’ end (proximal to codon 528) and at codon 1061 of APC. Of note, this group has also reported two patients with an APC mutation at codon 2092 who developed thyroid cancer. Therefore, mutations at the 3’ end may also increase the risk of thyroid cancer. As more data are collected, these will help to elucidate the genotype–phenotype correlation of thyroid cancer in FAP.

In the family evaluated in this report, neither of the two females with desmoids had colonic polyps, but both of the affected males had colonic polyposis. This intrafamilial phenotypic variation might be attributed to influences of modifier genes or environmental factors.

In conclusion, we identified a rare APC mutation in a desmoid tumor patient with a family history of AFAP with desmoids and thyroid cancer. This mutation results in the production of an APC protein with a truncation at the C-terminal distal end, which renders it incapable of suppressing the development of desmoids and thyroid cancer. In the diagnosis of AFAP patients with desmoids, mutation screening of not only the 5’ region but also of the 3’ region of the APC gene is necessary.

HGV DATABASE

The relevant data from this Data Report are hosted at the Human Genome Variation Database at http://dx.doi.org/10.6084/m9.figshare.hgv.578.

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