ELSEVIER

Polyposis Coli, Craniofacial Exostosis and Astrocytoma: The Concomitant Occurrence of the Gardner's and Turcot Syndromes

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Koot RW, Hulsebos JMM, van Overbeeke J. Polyposis coli, craniofacial exostosis and astrocytoma: the concomitant occurrence of the Gardner's and Turcot syndromes. Surg Neurol 1996;45: 213–8.

BACKGROUND
Up to 60% of the patients with known adenomatous polyposis coli may present hyperostosis of the skull and facial bones, and/or a susceptibility to fibromas. This is known as the Gardner's syndrome, and is considered as an allelic variant of familial adenomatous polyposis (FAP). Also, although very rare, an adenomatous polyposis coli may occur with malignant tumors of the central nervous system, known as Turcot syndrome. If both syndromes are different phenotypic presentation of FAP, this would explain a simultaneous occurrence.

METHOD
We report the history of a patient who showed clinical signs of the simultaneous occurrence of both Gardner's and Turcot syndromes. The syndromes are compared, and in view of the literature, a genetic explanation for the concomitant occurrence is discussed.

RESULTS
Evidence obtained from the literature to consider Turcot syndrome as a phenotype of FAP is as follows:

(1) The occurrence of Gardner's and Turcot syndromes in one family, but in different members;
(2) The presence of congenital hypertrophic retinal pigmented epithelium (CHRPE), which correlates with the expression of polyps in FAP patients, in both syndromes;
(3) Linkage of the Turcot phenotype to the adenomatous polyposis coli locus by genetic markers.

Evidence obtained from this case report indicates that there is a manifestation of both syndromes in one patient together with a positive family history for FAP.

CONCLUSION
This concomitant occurrence of both Gardner's and Turcot syndromes in one patient clinically supports genetic and ophthalmic investigation to consider Turcot syndrome (like Gardner's syndrome) as a phenotypic variant of FAP. Patients with FAP should be examined for the presence of Gardner's syndrome. In case a Gardner's syndrome is suspected, a computed tomography scan of the brain is recommended because of the possible existence of a simultaneous Turcot syndrome.

KEY WORDS
Polyposis coli, craniofacial exostosis, astrocytoma, Turcot syndrome, Gardner's syndrome.

Gardner's and Turcot syndrome are hereditary conditions with adenomatous polyposis coli in common. In addition to this gastrointestinal manifestation, the Gardner's syndrome presents with hyperostosis of the skull, skull base, or facial bones, and (sub)cutaneous lesions like epidermoid cysts or fibromas [4]. Desmoid tumors [6], various dental abnormalities [5], and extracolonic carcinomas [3,18] can also be part of the syndrome.

Turcot syndrome is known as the simultaneous appearance of adenomatous polyposis coli and malignant neuroepithelial tumors, in particular gliomas and medulloblastomas [24]. This syndrome is very rare; less than 50 patients have been described [8].

In this article, we present a patient who is likely to have both syndromes. Although the simultaneous presence of Gardner's and Turcot syndromes among members of one family has been described [11], the simultaneous occurrence of both syndromes in one patient has not previously been reported.

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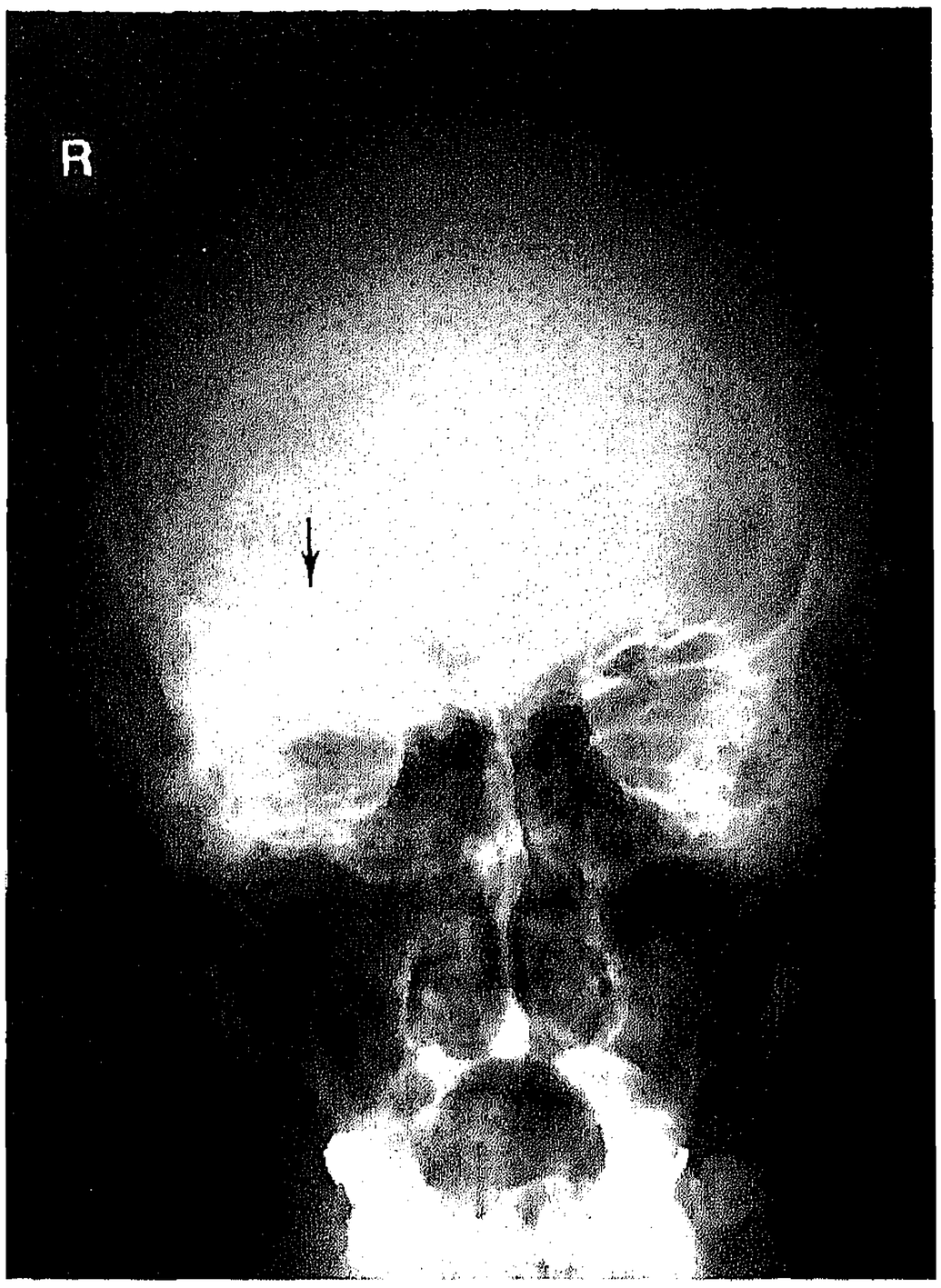
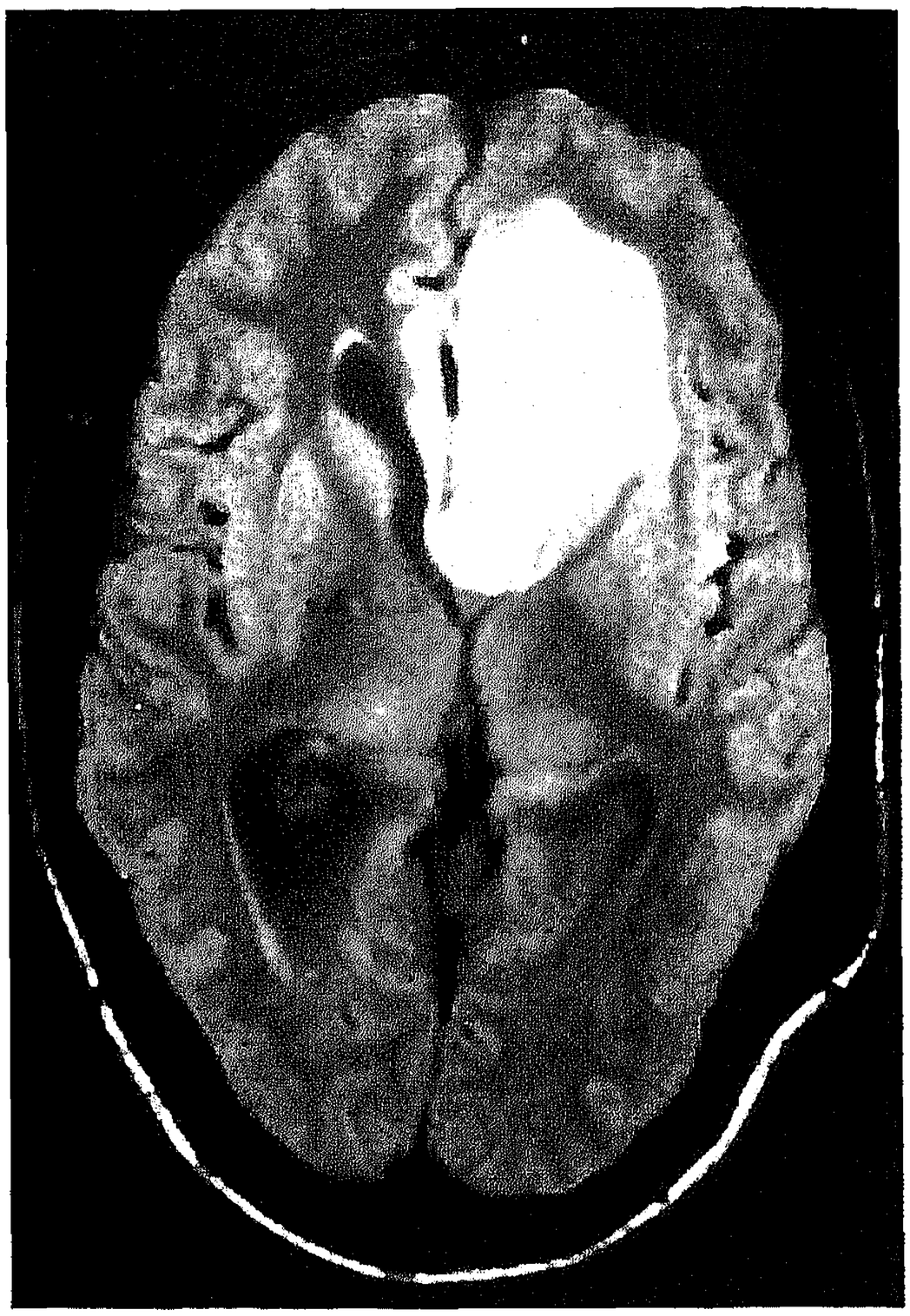
Received December 20, 1994; accepted July 17, 1995.

0090-3019/96/$15.00
SSDI 0090-3019(95)00380-0



1 X ray of skull: Hyperostosis of the right part of the skull base (*arrow*).



2 MRI of the brain (TR, 2080 ms; TE, 30 ms) showing a large area with increased signal intensity at the medial side of the left frontal lobe.

Case Report

A 19-year-old man complained of blood loss during defecation. Colonoscopy followed by colectomy revealed approximately 25 villous adenomas with a maximal size of 5 cm. Histologic verification showed marked adenomatous changes without infiltrative growth, corresponding to adenomatous polyposis coli.

Two months later, a relaparotomy had to be performed, as the small bowel was obstructed by extensive adhesions. Five months later, the patient complained of headache, nausea, and diplopia. Neurologic examination showed papilledema in both eyes and a slight right-sided facial palsy. At the left parietal region of the skull, a large bony elevation was found.

Plain x rays of the skull showed three lucent lesions in the parietal and frontal bone, and a large density on the left parietal bone and right skull base, which were suggestive of hyperostosis of the skull (Figure 1). The magnetic resonance imaging (MRI) scan showed a large hyperintensive intracerebral tumor in the left frontal lobe and an obstructive hydrocephalus (Figure 2).

A left-sided frontotemporal craniotomy was performed, and a large part of the tumor was removed. Histology showed a grade II protoplasmatic astrocytoma according to Kernohan [9]. Initially, the postoperative period was uneventful. However, 4 months later a ventriculoperitoneal drain was placed in the right frontal horn because of hydrocephalus. After that, the patient was able to perform his daily work.

Two years later, due to tumor recurrence and edema, a recraniotomy was done. Histology of the tumor was similar to the previously found grade II astrocytoma. In addition, radiotherapy was given to a total dose of 54 gray.

After an initial improvement, the patient deteriorated several months later. MRI investigation again showed growth tendency and edema at the original tumor location and also infiltration, tumor formation, and edema in the contralateral hemisphere. As no additional treatment could be offered, he died several months later.

At the time of the second operation, tumor cells were cultured for cytogenetic investigation, which did not show any chromosomal abnormality (apparently normal male karotype, 46 XY).

The family was screened for familial adenomatous polyposis coli. Colonic cancer was present in the paternal grandfather (died at 41 yrs), the pater-

1 Gardner's versus Turcot syndrome.

	GARDNER'S	THIS CASE	TURCOT
Mean age on presentation	27 years	19 years	19 years
Adenomatous polyposis	+	+	+
Average no. of polyps	1000	25	20–100
Size <5 mm	+++	+	+
Size >30 mm	–	+	+
Small intestine involved	+	–	–
Malignant transfer (years)	+	?	+
Osteomas	+	+	–
Gliomas of the central nervous system including medulloblastomas	–	+	+
Soft tissue tumors like epidermoid cysts, desmoid tumors, and fibromas	+	+	–
Various dental abnormalities	+	–	–
Extracolonic carcinomas (adrenal region and thyroid)	+	–	–
Congenital hypertrophic retinal pigmented epithelium (CHRPE)	+	?	+
Synonyms	Gardner-Richards Fitzgerald-Gardner Hereditary polyposis and osteomatosis.		Turcot-Després-St. Pierre Glioma-polyposis Colon polyposis CNS tumor.

Data are obtained from literature (see text).

nal father (died at 71 yrs), and the maternal father (died at 76 yrs). Neither the parent of our patient nor his older sister had signs of polyposis or colonic cancer. Adenomatous polyposis coli was only found in the patient's younger sister. Neither her neurologic condition nor the MRI scan shows any pathology until now.

DISCUSSION

In this patient, the following details were present:

(1) Adenomatous polyposis coli at an age of 19 years,
(2) hyperostosis of the skull and skull base;
(3) a low-grade astrocytoma in the left frontal lobe;
(4) extensive adhesions after laparotomy.

1. Both Gardner's and Turcot syndromes present an adenomatous polyposis coli [19]. The mean age of presentation of the Gardner's syndrome is halfway through the third decade [12], whereas in the Turcot syndrome it is at the end of the second decade [8]. The polyps of the Gardner's syndrome are identical to those in the familial adenomatous polyposis coli syndrome (FAP). They are small (almost always < 5 mm), numerous (average of 1000), and not restricted to the colon [2]. In Turcot syndrome, polyps are larger in size (frequently > 3 cm), less numerous (normally 20–100), and usually limited to the colon [7]. The polyps of both syndromes undergo malignant transformation, as a rule several years after the first gastrointestinal manifestations. The main symptoms and differences are summarized in Table 1.

   When the patient presented at the age of 19 years, approximately 25 adenomatous polyps (maximum size, 5 cm) were found. This atypical adenomatous polyposis coli corresponds most to Turcot syndrome.
2. Hyperostosis is a characteristic finding in the Gardner's syndrome. Separate tumors (osteomas) or protrusions from already existing bone structures, such as the skull and skull base as found in the presented patient, may occur. Mandible, sphenoid, and maxilla are also frequently affected [4]. These tumors rarely undergo malignant degeneration. In Turcot syndrome, there are no reports of such bone tumors.
3. Malignant tumors of the central nervous system are essential findings in Turcot syndrome. The syndrome should be restricted to those cases in which adenomatous polyposis coli is coupled with the brain tumors, as originally described by Turcot in 1959 [24], i.e., gliomas including medulloblastomas [8, 20]. The time between the gastrointestinal complaints and the onset of these tumors usually does not exceed 5 years. Neural

tumors, which present more that 20 years after the initial symptoms of adenomatous polyposis coli, must therefore be considered as coincidental tumors [8]. Low-grade astrocytoma, as in the presented patients, is a regularly found tumor in Turcot syndrome.

4. Mesenteric fibromatosis or desmoid tumor formation following abdominal surgery and leading to postoperative bowel obstruction is a well known symptom of Gardner's syndrome or FAP in general [6]. The etiology of the insufficient regulation of connective tissue growth is not clear, although (surgical) trauma, pregnancy, and other hormonal effects have been mentioned as contributing to the formation and growth behavior of these tumors [6]. A similar process with extensive adhesions was found in the patient we describe.

Summarizing, the type, number, and distribution of adenomatous polyps, together with a grade-2 astrocytoma are indicative of full-blown Turcot syndrome. However, hyperostosis and fibromatosis with adenomatous polyposis coli also present in the same patient, comply with the definition of Gardner's syndrome. So in this patient the clinical signs of Gardner's and Turcot syndrome occur simultaneously.

As both syndromes present an adenomatous polyposis coli, it may be relevant to find out whether Gardner's and Turcot syndromes are different phenotypic presentations of the familial adenomatous polyposis syndrome (FAP). If so, this would explain the simultaneous occurrence of both syndromes in the presented patient.

The Gardner's syndrome is an allelic variant of the FAP, as both syndromes show coupled transmission with the same markers at chromosome 5q [13]. After the adenomatous polyposis coli (APC) gene was mapped at chromosome 5q21 and cloned [10], it was found that both syndromes showed germline mutations at the APC locus [16]. FAP has an autosomal dominant mode of inheritance with high penetrance. For the Turcot syndrome, both an autosomal dominant and recessive mode of inheritance have been advocated, but because of the very low incidence of the syndrome, no common opinion of inheritance can be given yet.

In general, the number and size of the polyps differ in the Gardner's and Turcot syndrome. Nagase et al found a correlation between the location of the mutation in the APC gene at chromosome 5q, and the number of polyps in FAP patients has been reported [15]. One can imagine that the location of the mutation in the APC gene also influences the formation of the extracolonic (brain) tumors. This may reduce the Gardner's and Turcot syndrome to allelic variants of FAP caused by mutations at different locations within the APC gene. Some mutations may even give rise to a mixed phenotype, as in this case.

This theory is supported by the finding of congenital hypertrophic retinal pigmented epithelium (CHRPE) in a patient with a Turcot syndrome [14]. As the presence of CHPRE lesions correlates with development of polyps in both the FAP and the Gardner's syndrome [17,23], this also gives evidence to consider the Turcot syndrome as an allelic variant of FAP.

Several authors' observations of "polyposis coli" families in which the Gardner's and the Turcot syndrome occur in the same family, but in different members [11,20], also support this theory.

Regarding the patient's family, only the younger sister was affected by an adenomatous polyposis coli. It was known that the fathers of both parents and the paternal grandfather suffered from colonic cancer, but no additional information is available. Apart from his younger sister no neuroradiologic examinations of the family members were performed.

As a rule, syndromes with an autosomal dominant inheritance like FAP show a very variable expression. This means that a carrier of an abnormal or mutated gene need not always be recognized.

Therefore, the most obvious interpretation of this case would be a paternal familial inheritance of FAP, without penetrance or with a minimal expression in the father of the patient. The predisposing mutation in the APC gene may reveal both a Gardner's and Turcot phenotype.

By using a panel of FAP-linked DNA markers, Tops et al suggested that involvement of the APC gene at chromosome 5q21-q22 in the family of the presented patient was very unlikely [22]. However, the marker currently accepted for clinical determination of linkage to mutations at the APC locus (D5S346) [21] was not part of the markers that Tops et al applied in their study. Lasser et al used this nearest-to-the-APC-locus-located polymorphic marker in analyzing a 12-member family in which three individuals had Gardner's and two had Turcot syndrome [11]. Highly suggestive evidence for linkage of the Turcot phenotype to the APC locus was found in this study. Reexamination of the presented patient and his family by using marker D5S346 may also show evidence for linkage to the APC locus.

The concomitant occurrence of Gardner's and Turcot syndrome in one patient can be seen as the ultimate evidence for what was already plausible by

genetic [11] and ophthalmic [14] investigations, i.e., the Turcot syndrome being a variant phenotypic expression of the APC gene. In this respect, the patient's sister may develop a similar syndrome.

Based on the fact that after careful examination for extracolonic manifestations, 15%–60% of the patients initially presenting with FAP meet the criteria of Gardner's syndrome [1,2], supported by reports of Gardner's and Turcot syndrome in one family, we recommend a thorough physical and neurologic examination and plain x rays of the skull for these patients. A computed tomography scan (contrast enhanced) of the skull and brain is highly recommended in those patients with adenomatous polyposis coli in which osteomas are found during physical examination or on plain x rays of the skull.

Furthermore, children and young adults of a family with a history of FAP should have a complete ophthalmic examination as the finding of CHRPE patches indicates an increased risk for the development of gastrointestinal polyps and tumors of the central nervous system [14,23].

We thank EF Ippel, M.D., Ph.D., Institute for Antropogenetics, University of Utrecht, DA Bosch, M.D., Ph.D., and SG Leenstra, M.D., Ph.D., Department of Neurosurgery, Academic Medical Centre, for critically reviewing the document.

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polyposis of the colon. Dis Colon Rectum 1959;2: 465–8.

COMMENTARY

The authors describe a patient who had features of Gardner's syndrome and Turcot syndrome, in that the patient had adenomatous polyposis of the colon in addition to a left frontal lobe astrocytoma, Grade II (Turcot syndrome), and by plain x rays of the skull, left parietal bone and right skull-base hyperostosis (Gardner's syndrome). This is a most interesting case for the occurrence of these two syndromes, there was a positive family history in that the paternal grandfather died of colon cancer, and it was present in the paternal father and maternal father. Both parents of the propositus and his older sister were negative for colon cancer. The patient may have an autosomal recessive form of this disease complex and could represent a new and unique inherited form of astrocytoma. Additional studies for a mutation at 5q21q22 would be of great interest in this family as the gene for familial adenomatous polyposis coli has been mapped to that locus.

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An explosive growth in the field of medical genetics has occurred in the last years. The list of genes responsible for various human diseases and identified and studied at the molecular level increases monthly. This development brings about major revisions in thinking about some conditions that had been considered to be separate clinical entities. Mutations in different regions of the same gene can cause quite different symptoms. For instance, we now know that Duchenne muscular dystrophy and Becker muscular dystrophy result from mutations of different domains of the same gene. The same is true for a variety of craniosynostosis conditions described as Pfeiffer syndrome, Crouzon syndrome, Jackson-Weiss syndrome, and Apert syndrome [4]. These findings come from converging genetic evidence and careful clinical examination of marginal presentations of related syndromes. From this standpoint, the paper by Koot et al presents an important link between familial adenomatous polyposis (FAP), Gardner's syndrome, and Turcot syndrome. FAP is a widespread inherited condition. The gene responsible for FAP, the so-called APC-antioncogene, is located at the locus 5q22.1 and was cloned 4 years ago [2]. The function of the protein encoded by the gene is unknown. Gardner's syndrome is described as a variant of FAP with craniofacial malformations; Turcot syndrome is described as a variant of FAP with malignant tumors of the central nervous system. There are data that show that Gardner's syndrome maps to the same location on chromosome 5 [1] as does Turcot syndrome [3]. Another symptom that occurs concomitantly with FAP and is determined by mutations in the ACP gene is congenital hypertrophy of the retinal pigment epithelium (CHRPE), and the expression of this symptom was correlated with specific mutations in the APC gene [5]. There is a good chance that all the conditions listed above are caused by mutations in the same gene. The paper by Koot fills the missing clinical link, demonstrating that these can occur together. The paper strongly suggests monitoring patients with any manifestations of these three syndromes for other related symptoms, and this recommendation is supported by genetic evidence.

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