Short Communication

Aggressive mutation in a familial adenomatous polyposis syndrome family: when phenotype guides clinical surveillance

Florencia Neffa[1], Lucia Garcia[1], Adriana Della Valle[1], Florencia Carusso[1], Carolina Vergara[1], Daniel Sanchez[3], Marta Sapone[1], Noelia Silveyra[3], Ana Laura Revello[3], Patricia Esperon[1,2]

[1]Grupo Colaborativo Uruguayo, Hospital Central de las Fuerzas Armadas, Montevideo, Uruguay; [2]Laboratorio de Genética Molecular Facultad de Química, Universidad de la República, Montevideo, Uruguay; [3]Instituto Nacional del Cáncer, Montevideo, Uruguay

Correspondence to: Florencia Neffa. Grupo Colaborativo Uruguayo, Hospital Central de las Fuerzas Armadas, Montevideo, Uruguay.
Email: floneffa@gmail.com.

Abstract: Familial adenomatous polyposis (FAP) is an autosomal dominant genetic condition, caused by mutations in the adenomatous polyposis coli *(*APC*)* tumor suppressor gene. Desmoid tumors (DTs) are seen in 15% to 20% of FAP patients. Specific location of mutation serves as a guide to predict colonic and extra colonic manifestations and their aggressiveness. A severe FAP-phenotypic family was registered in a genetic counselling high-risk Uruguayan hereditary cancer clinic. Proband's DNA was analysed by NGS, detecting a pathogenic mutation in APC gene. All willing family members were counselled and encouraged to be tested. Here we report a kindred formed by 16 individuals with a very severe FAP phenotype. A two-base deletion mutation: c.4393_4394delAG in APC gene and a consequent premature stop codon was detected. DTs were diagnosed in 6 individuals, ranging from 2 to 25 years of age. The causes of death were diverse: gastric cancer, rectal cancer and desmoid tumor. The already described genotype-phenotype correlation has proved its worth in this family, as clinical features reflect the mutation location at 3' end of *APC* gene. The inheritable and lethal nature of the disease needs a tailored follow up approach in order to reduce mortality, optimize local tumor control, and preserve patients' quality of life.

Keywords: Familial adenomatous polyposis (FAP); desmoid tumor; phenotype; adenomatous polyposis coli gene (APC gene)

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Background

Familial adenomatous polyps (FAP) is an autosomal dominant genetic condition, caused by mutations in the adenomatous polyposis coli gene (APC) located in chromosome 5q21. Less than 1% of colonic hereditary cancer is explained by a mutation in the APC gene (1,2).

The APC protein has multiple designated segments that make possible its multiple cellular functions and plays a major role in tumor suppression, by antagonizing the WNT signaling pathway; and in preventing cell overgrowth.

Classical FAP has been historically characterized by the presence of more than a hundred adenomatous polyps, distributed in both upper and lower gastrointestinal tract. The variants of FAP are distinguished by the number of polyps or by extra-colonic manifestations (3).

Desmoid tumors (DTs), found in 15% to 20% of FAP patients, being considered as an aggressive form of neurofibromatosis, are defined as locally infiltrating musculo aponeurotic neoplasms derived from connective tissue (4). The growth rate could be colossal. It's enlargement is frequently the cause of organ compression causing clinical complications and, in some cases even death (5). DTs are classified as: (I) abdominal (anterior abdominal wall); (II) intra-abdominal (mesentery or pelvis, intraperitoneal or retroperitoneal), site of preference, as seen in almost 50%

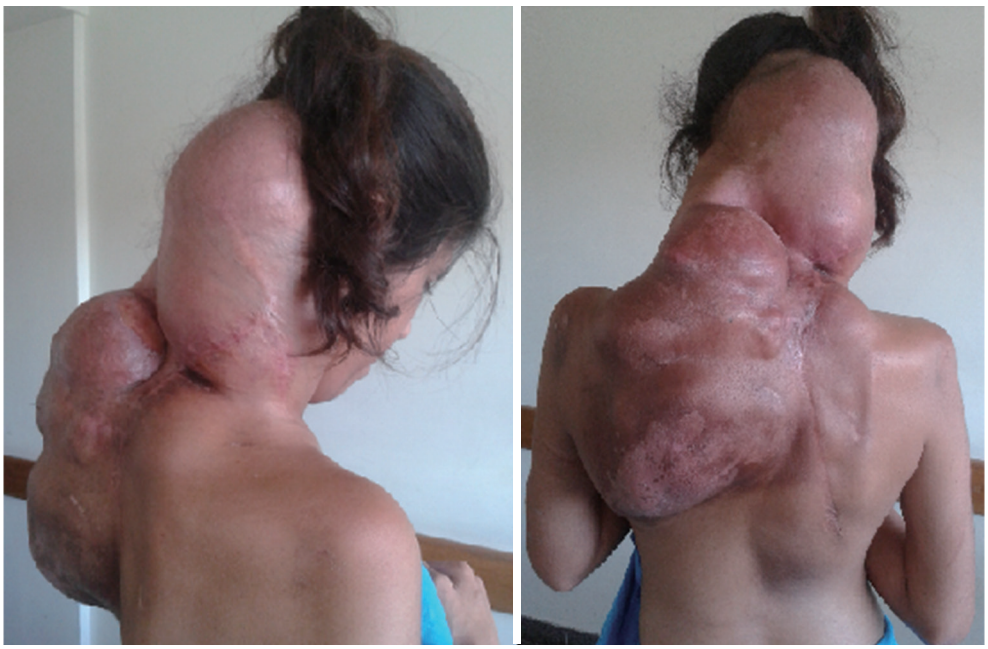

Figure 1 DT of the female proband, situated from the inferior line of the left scapular joint to skull base, compressing the aero digestive carrefour. DT, desmoid tumor.

of cases; and (III) extra-abdominal (chest, head and neck region and extremities) (6,7).

Polyps usually present during young adolescence, whereas cancer diagnosis frequently appears in young adulthood. Extra-colonic malignancies are also part of the syndrome, such as: papillary thyroid cancer (2–3%), hepatoblastoma (1–2%), medulloblastoma; (<1%), pancreatic (1%), gastric (1–2%), and duodenal cancer (4–12%) (8). FAP associated-gastric lesions are: fundic gland polyps, gastric adenomas, and gastric cancers.

The main death causes in these patients regarding extra-colonic lesion are as follows: desmoid tumours (9.9%), duodenal cancer (5.6%), and gastric cancer (2.8%) (9).

A genotype-phenotype correlation in FAPs was described for the first time in 1992 (10).

The association between certain extra-colonic manifestations and the locus of the APC mutation, reflects the role that the APC protein plays in different tissues, the age of onset and severity of the disease in those mutations located further from 3' of the APC gene (11). Although a genotype–phenotype correlation was described, an important variability among patients, even among family members, makes us think that the effect of APC-modifying genes and/or environmental factors may influence the expression of the disease.

The aim of this article is to present and analyse a case of a severe, early onset family presenting with lethal extra-colonic manifestations.

Patients and methods

Patients

The proband, a female patient (II.7) was diagnosed with a left scapular joint soft tissue DT at the age of 20 (*Figure 1*). From then onwards, she was operated on and then even received polychemotherapy (PQT), reaching tumor stability evidenced in magnetic resonance imaging (MRI) months later (*Figure 2*).

At 21 she developed tumor progression, severe pain with neuropathic component, resistant to pain management and she underwent surgery for tumor mass-reduction, including muscles from the paravertebral leak. Due to a local tumor recurrence, she was once again surgically treated at age 22. The first-line chemotherapy consisted on 4 cycles of liposomal doxorubicin, not showing much progress. For second-line chemotherapy 5 cycles of Crisafeno, also not entirely successful.

At 23 years old, the tumor progression was again confirmed, and a systemic treatment based on liposomal

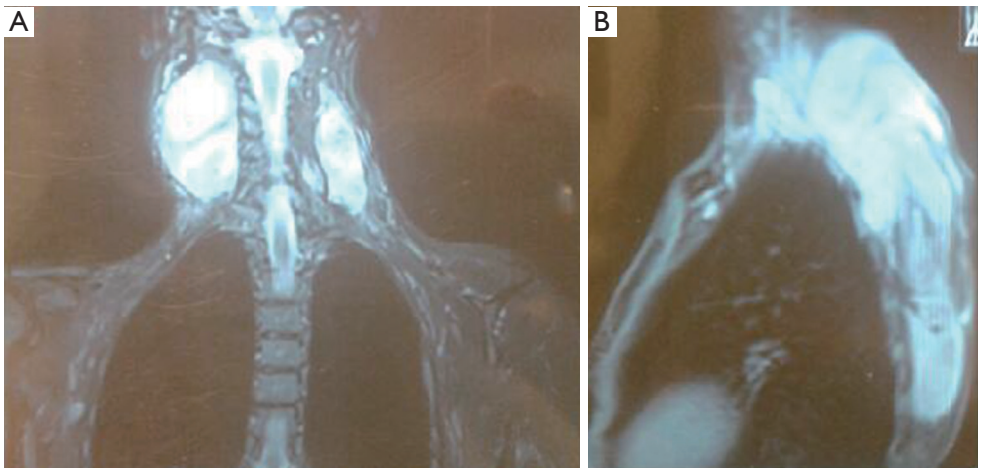

Figure 2 Probands cervicothoracic MRI. (A) Anterior coronal view; (B) axial view. The arrows indicate the DT. DT, desmoid tumor.

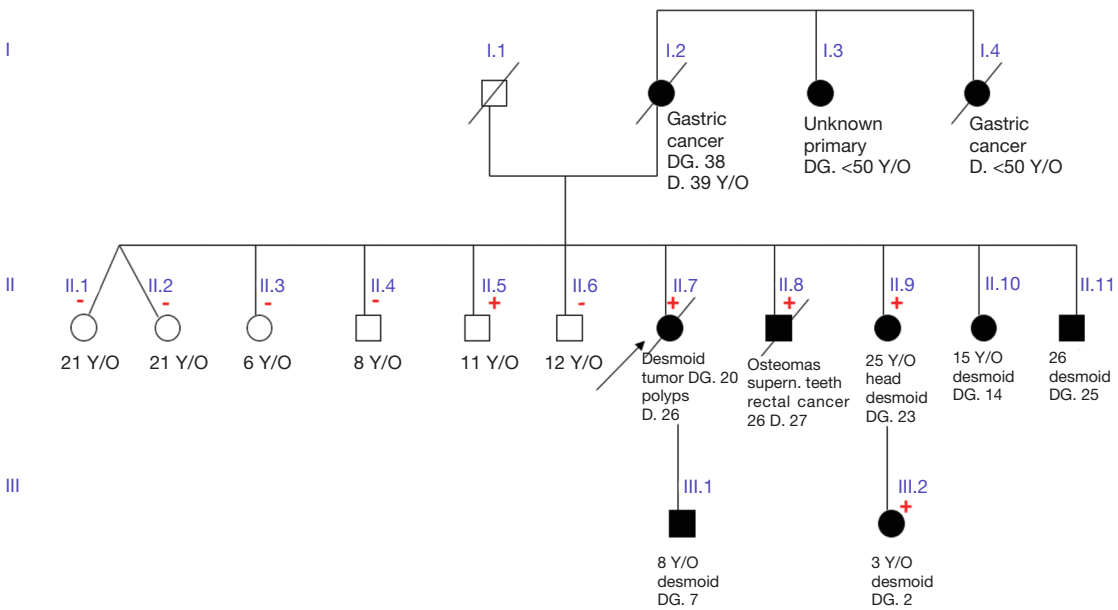

Figure 3 Genealogy of the FAP kindred. (+), mutation carrier; (–), non-mutation carrier; D, death age; DG, diagnosis age; the arrows indicate the proband status. FAP, familial adenomatous polyposis.

doxorubicin was administered intermittently during two years, when she was re-intervened. As third-line chemotherapy a combination of Methotrexate and Vinblastine was provided.

At 26 treatment shifted to a palliative PQT and radiotherapy (RT), starting with 4 cycles of liposomal doxorubicin, continuing with cyclophosphamide prophylaxis, showing tumor remission. The RT was interrupted due to radiodermatitis and skin infection.

Her fists control endoscopy revealed 22 gastric polyps and colonic mucosae compatible with multiple polyposis [50–100]. Non-malignant features such as supernumerary teeth and head osteomas were also identified. Finally, she was referred to a genetic counselling. At 27, she died due to desmoid tumor progression.

Proband's and relative's medical records were gathered from different health care centres and a genealogy was constructed (*Figure 3*).

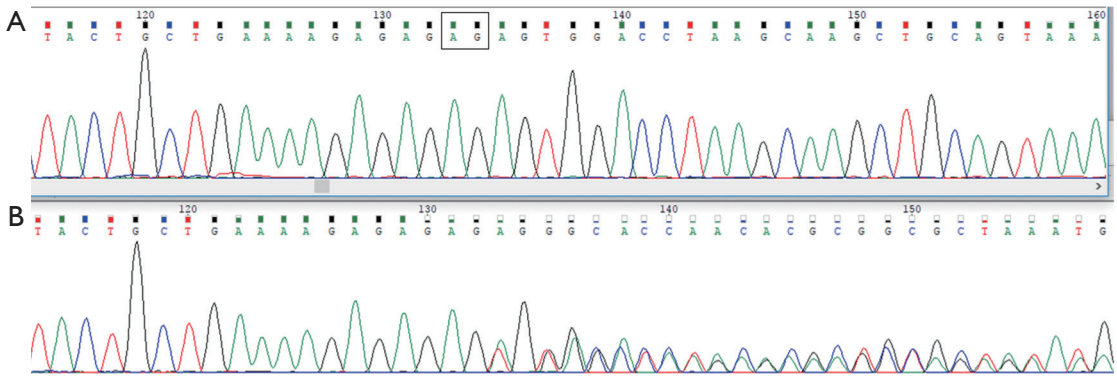

Figure 4 Electropherogram of Sanger analysis showing: (A) normal sequence, and (B) 2bp-deletion at position c.4393-94 of the APC gene. The rectangle remarks the (AG) deleted nucleotides. APC, adenomatous polyposis coli.

Informed consent was previously taken from all consenting adults and minors' legal tutors when necessary.

For all individuals who chose to be counselled and tested, the Uruguayan Collaborative Group (UCG), committed to register, diagnosis and investigate hereditary cancer syndromes, conformed by a multidisciplinary team of experts, conducted the high risk assessment consults and absorbed the genetic testing financial burden, through a fund raising foundation (www.fundaciongenesis.org.uy).

Methods

DNA from the probands oral mucosa was obtained using commercial Kits. Analysis was made with Next Generation Sequencing (NGS).

Sanger sequencing was offered to all family members willing to be tested.

Results

From a family composed by 16 members, ten were tested, three did not adhere to surveillance program and chose not to be tested, and three were dead before the genetic counselling high risk assessment began (two gastric cancer and one rectal cancer victims). Genetic counseling was performed pre and post-test. Using the NGS technology a 2-bp deletion (c.4393_4394delAG) at 3'end of APC gene was detected. Sanger sequencing confirmation was later done (*Figures 4,5*).

Six individuals presented DTS. The median age for DT diagnosis was 15.2 (±9.2) years, ranging from 2 to 25. Clinical characteristics are described in *Table 1*.

There is a very clear anticipation phenomenon pattern, given by successive earliest ages of diagnosis for the third generation (*Table 1*).

In five patients, a pathogenic, heterozygote mutation, located in the APC gene was detected. Four of the individuals were carriers of DTs, the remaining mutation carrier is an asymptomatic 11 years old boy. None of young family members has undergone endoscopic examination.

Discussion

Here we presented a case that follows an autosomal dominant transmission pattern. It was caused by an APC germline AG deletion at 1,465 codons with a penetrance near 100% for DTs, and a very clear anticipation phenomenon. The presence of a relatively small number of colonic polyps found in two out of five mutation carriers (II.7 and II.8), indicates that the codon 1,465 frameshift mutation is incompletely penetrant in the GI tract, which is evidenced by a late-onset and attenuated forms of polyposis.

DTs are benign extra-intestinal lesions associated with colonic polyposis, which can turn into a serious or mortal complication for FAP individuals.

To date, there is not enough evidence for a clear genotype-phenotype correlation to DTs severity and incidence. They are mostly associated with mutations between codons 1,250 and 1,400 of the APC gene that mainly end in a truncated protein (15,16). According to Caspari *et al.*, mutations located between codon 1,445 and 1,578 result in DTs, among other manifestations (osteomas, epidermoid cysts, and polyps of the upper GI tract) (17). The phenotypic variability may lay on the two-hit

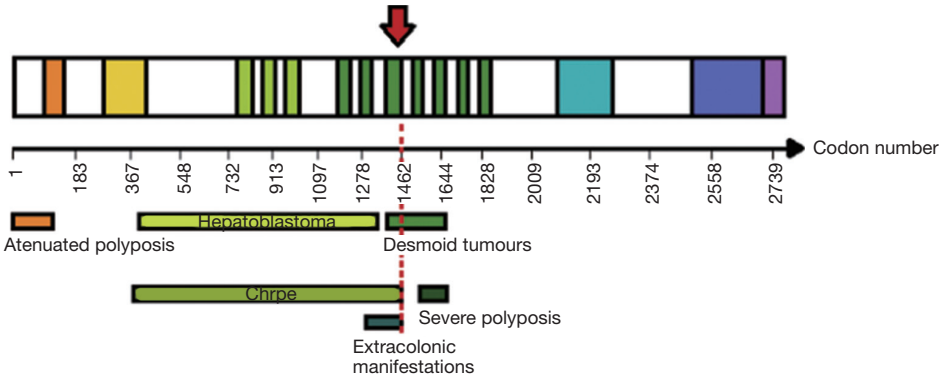

Figure 5 APC gene illustration showing genotype-phenotype correlation. The red arrow shows the location of the pathogenic mutation the family described above carries. This mutation clinically manifests mostly with DTs. A correlation between disease severity and the location of the mutation on the APC gene was proposed as follows: attenuated FAP is correlated with mutations before codon 168 (5 end), after codon 1580 or in the alternatively spliced region of exon 9, and severe polyposis (>1,000 adenomas) with mutations between codons 1250 and 1464. In the intermediate phenotype, classic FAP, mutations are located in the remainder of the APC gene, in particular the 5'end. Extra-colonic manifestations, as DTs are more likely associated with certain regions of the APC gene mainly with mutations at the 3'end (12,13). More specifically, mutations after codon 1464 or codon 1493 were associated with a 20-fold higher risk for extra-abdominal DTs (14).

Table 1 Family identification number (ID); clinical diagnosis; age at diagnosis; and carrier status for the APC known pathogenic mutation, are schematize

ID	Diagnosis	Age at diagnosis	Carrier status
I.2	Gastric cancer	38	Not tested
I.3	GI tumour (unknown primary)	<50	Not tested
I.4	Gastric cancer	<50	Not tested
II.1	–		Negative
II.2	–		Negative
II.3	–		Negative
II.4	–		Negative
II.5	–		Positive
II.6	–		Negative
II.7	Desmoid, osteomas, supranumerary teeth Gastric and colonic polyps (<100)	20	Positive
II.8	Rectal cancer, osteomas, supranumerary teeth. Multiple adenomatous polyps (<100 polyps)	26	Positive
II.9	Desmoid (dorsal topography <5 cm)	23	Positive
II.10	Desmoid (dorsal topography <5 cm)	14	Not tested
II.11	Desmoid (dorsal topography <5 cm)	25	Not tested
III.1	Desmoid (dorsal topography <5 cm)	7	Not tested
III.2	Desmoid (dorsal topography <5 cm)	2	Positive

mechanism.

The mutation causes a premature translation stop, therefore, a shortened APC protein: p.S1465WfsX3. This mutation has been previously reported (18,19).

In this family group, the mutation in codon 1,465 of *APC* gene is associated to a phenotype consisting in blossoming DTs located in dorsal region, with relatively low polyposis burden. Although the mechanisms of this variability must still be elucidated, it can be possible that a different modifier gene favored the 'second hit' in mesenchymal cells (in II.7), or in gastric cells (II.8) producing the typical GI or desmoids tumors, respectively (20,21).

The National Comprehensive Cancer Network emphasises that there is not enough data to support specific screening and treatment for DTs [hormone therapies, no steroidal anti-inflammatory drugs (NSAIDs), targeted therapies, and traditional cytotoxic chemotherapies]. The recommendations encourage physicians to make individualized surveillance to account for genotype, phenotype and personal considerations (22). The absence of more precise guidelines has motivated our group (UCG) to state some considerations for a more adequate patient management.

Once a patient is clinically diagnosed as FAP, a genetic study must be performed since the genotype helps guide surveillance. Although there is some heterogeneity in clinical manifestations of FAP, even among family members with the same APC gene mutation, the correlation between the site of the mutation within the gene and the clinical manifestations of the disease is useful for the clinical management of affected patients (23,24). A multidisciplinary approach with different individualized treatments should be extremely beneficial. Patients with desmoids located in the head and neck region that could became in life-threatening complications need more aggressive and prompt treatment (25). RT in combination with surgery results in better local control than surgery alone, even in recurrent DT (26). Evidence for the efficacy of treatments is limited because it's based on small, non-controlled studies. The small number of cases in even major tumor centers has limited the ability to better study patients with DTs (27).

In conclusion, for overall better management and outcome, it is imperative to offer genetic counseling risk assessment and tailor surveillance for each family member, according to: risk profile, age, comorbidities, mutation site and access to healthcare. It should also be performed in specialized centers.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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