Am. J. Hum. Genet. 50:988–997, 1992

Phenotypic, Cytogenetic, and Molecular Studies of Three Patients with Constitutional Deletions of Chromosome 5 in the Region of the Gene for Familial Adenomatous Polyposis

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Summary

We have studied three patients, one with extensive polyposis of the colon, who have constitutional interstitial deletions of the long arm of chromosome 5. High-resolution banding studies indicated that the deletion in the patient with polyposis spans the region 5q21-q22, which includes *APC,* a gene involved in familial adenomatous polyposis and sporadic colon cancer. Molecular analysis with probes for sequences flanking *APC* confirmed this conclusion. The deletions in the other two patients, who are too young to have developed polyposis, had breakpoints within this region, precluding the use of cytogenetic analysis alone in making definitive predictions about their risks. Molecular studies resolved the uncertainty; in situ and quantitative Southern hybridizations of four probes for polymorphic segments revealed that one of the patients has a deletion of *MCC,* a gene which is approximately 150 kb proximal to *APC,* and two flanking markers. He is at increased risk for polyposis, while the other patient is not. The physical descriptions of these patients, in conjunction with cases in the literature, begin to allow delineation of two distinct 5q- syndromes. These studies also provide precise physical mapping data for *D5S71, D5S81, D5S84,* and *MCC* on 5q.

Introduction

Interstitial deletions of the middle portion of the long arm of chromosome 5 are relatively rare constitutional abnormalities. Because the banding pattern of this region is repetitious at average levels of resolution, most of the deletions that have been identified are poorly characterized cytogenetically. Consequently, phenotypic correlations with this heterogeneous group of deletions are not well defined. Delineation of the phenotypes and resolution of the individual deletions are important, since some of these patients will be at risk of developing colon cancer.

Received August 8, 1991; final revision received January 10, 1992.

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0002-9297/92/5005-0012$02.00

Prompted by the report of a single patient with polyposis and a 5q deletion (Herrera et al. 1986), a gene (*APC*) associated with familial adenomatous polyposis (FAP) was localized by virtue of linkage to polymorphic markers in the region 5q21-q22 (Bodmer et al. 1987; Leppert et al. 1987). FAP is a rare dominantly inherited disease in which affected individuals develop hundreds to thousands of colonic polyps, beginning in the second or third decade of life. One or more of these polyps invariably progress to carcinoma unless prophylactic colectomy is performed. Allelic loss of markers in the *APC* region is also one of the early steps in the genesis of sporadic colon cancer (Solomon et al. 1987; Vogelstein et al. 1988; Sasaki et al. 1989). The mechanism by which the *APC* product functions does not appear to be that of a classic recessive tumor suppressor, but, rather, it may act in a dominant-negative fashion (Fearson and Vogelstein 1990). Kinzler et al. (1991*b*) have recently identified a gene, *MCC,* which is mutated in sporadic colorectal cancer. Approximately 150 kb distal to *MCC* is the structurally related *APC,* which is mutated in both

sporadic cancers and FAP (Groden et al. 1991; Joslyn et al. 1991; Kinzler et al. 1991*a*; Nishisho et al. 1991).

We describe (*a*) the physical features of three patients with constitutional deletions of chromosome 5 and (*b*) the high-resolution chromosome and molecular studies that we performed in order to identify those individuals at risk for polyposis and colon cancer. This work serves as an example of how cytogenetic and molecular analysis can be combined in the analysis of chromosome abnormalities and their phenotypes.

Material and Methods

Chromosome Analysis

High-resolution banding studies (Francke and Oliver 1978) were performed on phytohemagglutinin-stimulated peripheral blood lymphocytes after 17 h of synchronization with methotrexate and 5 h of thymidine release, including ethidium bromide treatment for the final 2 h. Pairs of chromosomes 5 of at least the 550-band stage or longer were examined. The in situ hybridization of tritiated probes to the chromosomes of one subject (EC) also employed synchronized lymphocytes without the ethidium bromide treatment, but the other in situ hybridizations were to chromosomes of Epstein-Barr virus–transformed cells, according to a method described elsewhere (Yang-Feng et al. 1985). Emulsion exposures were 13–19 d.

Molecular Analysis

Five probes from the long arm of chromosome 5 were used in the Southern blotting experiments. C11p11, MCC_{58-104}, YN5.48, MC5.61, and pHp3 recognize the loci *D5S71, MCC, D5S81, D5S84,* and *ADRB2,* respectively, which map in that order, with *D5S71* the most proximal and *ADRB2* the most distal (Nakamura et al. 1988; Tops et al. 1989; Dunlop et al. 1990). In addition, probe VP57–1, which is from the short arm of chromosome 17 and which recognizes the *SYB2* locus, was used as a control. Only C11p11 and MC5.61 were hybridized in situ. C11p11 is a 3.6-kb *Eco*RI fragment cloned in pUC8 (Bodmer et al. 1987); YN5.48 is a 2.4-kb *Taq*I fragment in the *Acc*I site of pUC18; MC5.61 is a 3.5-kb *Eco*RI/*Hin*dIII fragment in pUC18 (Nakamura et al. 1988); pHp3 is a 2-kb human cDNA fragment encoding the beta-2-adrenergic gene, *ADRB2* (Yang-Feng et al. 1990); and VP57-1 is an M13 clone containing exon IV of the synaptobrevin 2 gene, *SYB2* (Archer et al. 1990). MCC_{58-104} is a 138-bp PCR amplification product of the *MCC* gene's first exon, which encodes amino acids 58–104 (Kinzler et al. 1991*b*). The probe was made with primers 5′-GAATTCATCAGCACTTCT-3′ and 5′-CAGCTCCAAGATGGAGGG-3′, by using the following amplification conditions: 94°C for 1 min, 55°C for 2 min, and 70°C for 2 min. The amplification product was excised from a 1% agarose gel and was purified through a spin column.

For Southern analyses, DNA samples were digested with restriction endonucleases, were separated on 0.8% agarose gels, and were transferred to nylon membranes (Hybond; Amersham). The probes were ^{32}P-labeled and hybridized according to methods described elsewhere (Lehrman et al. 1985; Barton et al. 1986). The Ambis Radioanalytic Imaging System (AMBIS System software, Peak extraction) was used for the quantitative analysis of the beta-emissions (6–16 h) from ^{32}P-labeled probes hybridized to genomic DNA fragments on Southern blots.

Case Reports

Patient SD (fig. 1, *top*) was referred for fragile-X testing at age 13 years because he is mildly mentally retarded and has a prominent jaw. He was born after 38 wk of gestation complicated by severe toxemia. Birthweight was 3,770 g, and Apgar scores were 5 and 6. His growth has followed the 25th –50th percentile for height and weight, while his older sibling and his parents are at the 95th percentile for height. On physical examination, patient SD displayed mild facial dysmorphism with a prominent forehead, hypertelorism, depressed nasal bridge, bulbous nasal tip, anteverted nostrils, wide philtrum with well-demarcated folds, prognathism, slightly posteriorly rotated ears, an upper lip with cupid's bow configuration, and high-arched palate.

When cytogenetic and molecular studies suggested that patient SD's deletion may include the *APC* locus, he was evaluated for signs of polyposis or Gardner syndrome. (Gardner syndrome is a condition thought to be allelic to FAP and is characterized by various benign tumors, such as lipomas, osteomas, and fibromas, in addition to multiple adenomatous polyps of the colon [Gardner 1972].) He was asymptomatic except for chronic constipation. Abdominal and rectal examinations were normal, as was a barium enema. Colonoscopy revealed a single benign polyp with focal atypia of the surface epithelium. No mandibular osteomas were detectable by x-ray. No cutaneous soft-tissue masses were observed initially, but 1 year later two large epidermoid cysts were removed from his

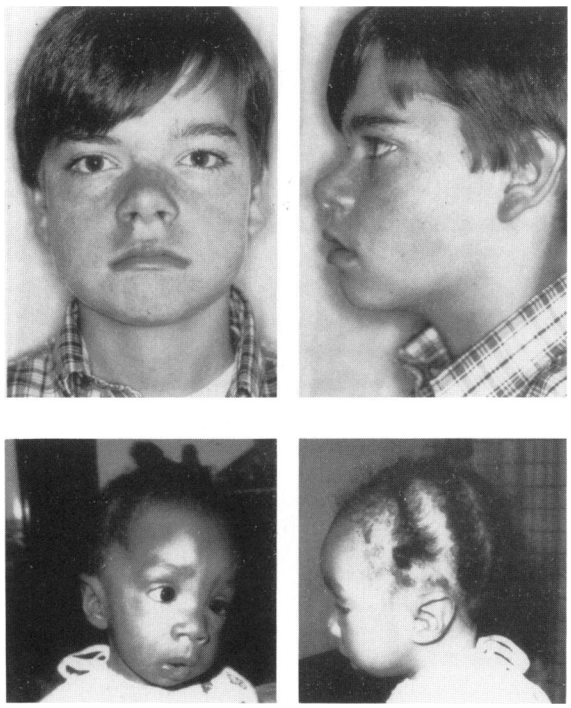


Figure 1 *Top,* Front and side views of patient SD at age 13 years. *Bottom,* Patient CC at age 8 mo.

legs. Ophthalmologic evaluation revealed bilateral small posterior pole cataracts and hypoplastic optic disks, but no lesions suggestive of congenital hypertrophy of the retinal pigment epithelium were detected.

Patient CC (fig. 1, *bottom*) was referred at age 8 mo for severe developmental delay, strikingly dysmorphic features, and failure to thrive. The prenatal history was significant for polyhydramnios and decreased fetal movement. He was born at term with Apgar scores of 3 and 8 and weighed 2,750 g. He was noted to have bilateral club feet, dislocated hips, camptodactyly, and unusually folded ears. At 5 wk of age he underwent bilateral herniorrhaphy and orchiopexy. At the time he was anemic and had mitral regurgitation with left atrial enlargement. He has since exhibited feeding problems and poor growth and poor development. A muscle biopsy to evaluate his marked hypotonia was normal, and a renal ultrasound study showed structurally normal kidneys.

Physical examination revealed that patient CC's height, weight, and head circumference were below the 5th percentile. His skull was unusually shaped, with biparietal prominence, a high prominent forehead, and hypoplastic supraorbital ridges. His dysmorphic facial features included hypertelorism, down-slanting palpebral fissures, epicanthal folds, broad and flat nasal bridge, anteverted nostrils, long and poorly defined philtrum, small mouth, high-arched palate, micrognathia, and slightly low-set posteriorly rotated ears that are abnormally folded and pointed. His neck was short. His nipples were widely spaced, and a systolic murmur was audible along the left sternal border. The anus was slightly displaced anteriorly. His extremities were extremely thin as a result of decreased muscle mass. His fingers continued to show mild camptodactyly, and he had a bridged transverse crease on the left palm.

Patient EC was studied at 30 years of age, after a colectomy. At birth she weighed 3,900 g and was noted to have small ears with abnormal folding. In infancy and childhood she was characterized as floppy, inactive, and profoundly retarded. She suffered from a seizure disorder that was not investigated. She had horizontal and rotary nystagmus and alternating strabismus, and her feet showed metatarsus varus deformity. She has been institutionalized since the age of 5 years. Both ovaries were removed subsequent to the discovery that one of them was polycystic. She has refractory anemia. She is partially deaf and unable to speak or follow simple commands.

None of us has had the opportunity to examine patient EC, and efforts to obtain a photograph of her have not been successful. However, she has been described as having dysmorphic facies. After a 10-year history of bleeding rectal and colonic polyps, she recently underwent a colectomy. Her bowel was studded with approximately 300 adenomatous polyps with high-grade dysplasia. There was no evidence of invasive carcinoma.

Results

Chromosome Studies

Chromosome analysis revealed an interstitial deletion of the long arm of chromosome 5 in all three patients (fig. 2). The deletion in patient SD is relatively small and extends from q15 to q21.3 (del(5) (q15q31.3)). Patient CC's larger deletion has removed the region from q22.3 to q31.1 (del (5) (q22.3q21.1)), which is distal to and does not overlap with the deletion in patient SD. The deletion in patient EC extends from q15 to q23.2 (del (5) (q15q23.2)), overlapping the entire deletion in patient SD and the proximal third of patient CC's deletion. Patient EC has a second chromosome rearrangement (not shown), which is a di-

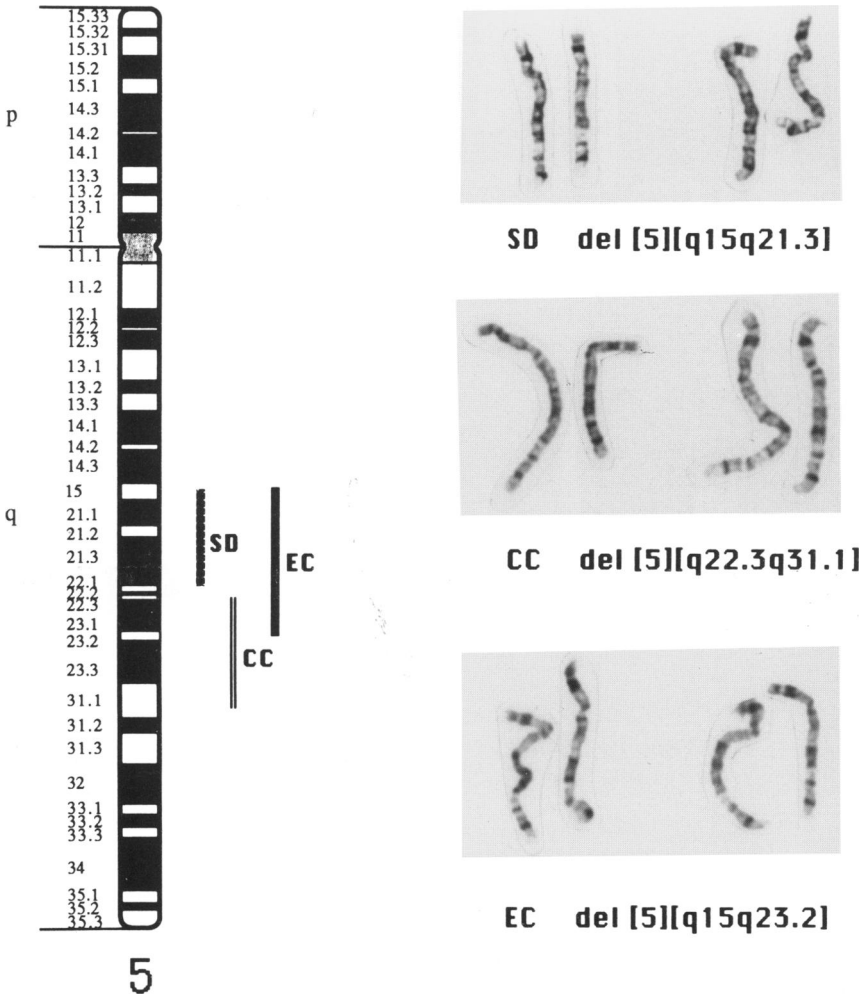


Figure 2 Pairs of chromosomes 5 of patients SD (*top*), CC (*middle*), and EC (*bottom*), with the abnormal chromosome on the right in each pair. The ISCN ideogram (*left*) of chromosome 5 shows the deleted segments (vertical bars), as determined on the basis of the interpretation of high-resolution GTG banded chromosomes.

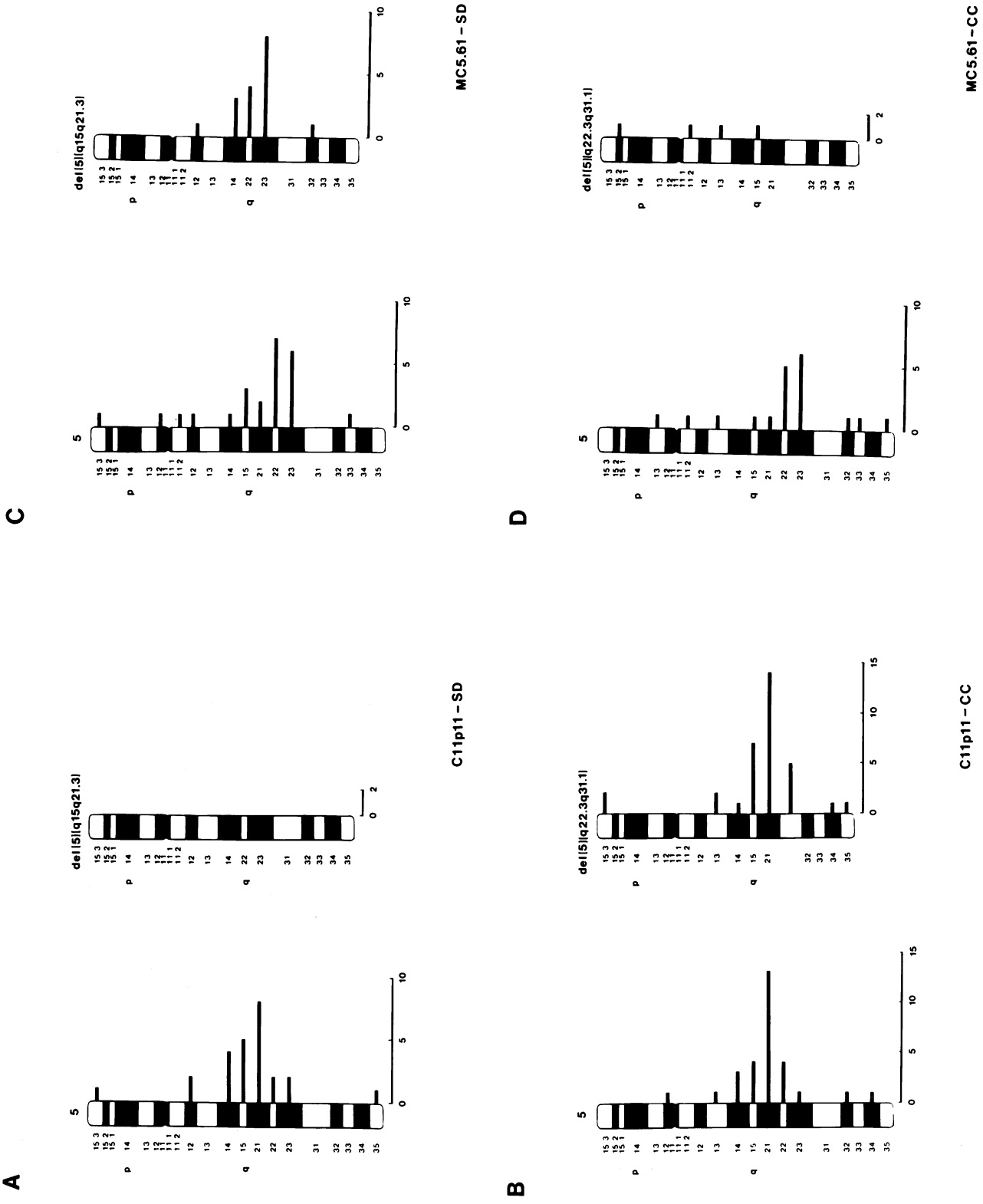
rect insertion of bands q14.2 to q21 of chromosome 11 into the short arm at band p13 (dir ins(11)(p13q14.2q21)). Each of these abnormalities is de novo, as all six parents have normal lymphocyte chromosomes.

Molecular Studies

A combination of in situ and Southern hybridizations, which characterize the deletion on the molecular level, were performed. The probes used in these analyses hybridize with loci mapped to chromosome 5 in the following order: centromere–*D5S71*(C11p11)–15cM or greater–*MCC*–1 to 3 cM–*D5S81* (YN5.48)–5 cM–*D5S84*(MC5.61)–*ADRB2* (pHp3)–telomere (Kobilka et al. 1987; Nakamura et al. 1988; Tops et al. 1989; Dunlop et al. 1990; Kinzler et al. 1991*b*). *APC* had not yet been cloned at the time this work was performed.

Two probes for sequences flanking the *APC-MCC* region—C11p11 and MC5.61—were chosen for the in situ hybridizations to chromosome spreads of the patients. These experiments established that a portion of the region is missing in all three patients and that these sequences are missing from the deleted chromosomes 5. As predicted on the basis of the cytogenetic analysis, the deleted chromosome 5 of patient EC did not hybridize with either C11p11 or MC5.61, nor did her abnormal chromosome 11 hybridize to them (data not shown). Therefore, her deletion is of the entire region from *D5S71* to *D5S84*.

The deletions in patients SD and CC do not extend


A
C11p11-SD
del(5)(q15q21.3)
B
C11p11-CC
del(5)(q22.3q31.1)
C
MC5.61-SD
del(5)(q15q21.3)
D
MC5.61-CC
del(5)(q22.3q31.1)

over the entire region (fig. 3). Patient SD's chromosome 5 does not contain the *D5S71* sequence but does contain the more distal *D5S84*. Conversely, patient CC's chromosome 5 carries *D5S71* but has a deletion of *D5S84*. Quantitative Southern analysis using C11p11, MC5.61, and control probe pHp3 for hybridization to *Pvu*II- and *Taq*I-digested DNA samples from patients SD and CC and from their parents was consistent with the in situ results (fig. 4; data not shown).

Whether the *APC-MCC* region is included in the deleted portions was determined by Southern analysis using probes for *MCC* and *D5S81*, in addition to a probe for *SYB2* on chromosome 17 as a control. The results with MCC_{58-104} (fig. 5*A*) indicate the presence of this sequence on both chromosomes 5 of each of the individuals, except for patient SD, who has only one copy. Patient CC's deletion does not include *MCC*. The same filter was rehybridized with VP57-1 (*SYB2*) and YN5.48 (*D5S81*) (fig. 5*B*), the latter of which maps within 3 cM distal to the *APC-MCC* region. We conclude that patient SD is hemizygous for *D5S81* while patient CC has two copies. Thus, patient SD's distal breakpoint is between *D5S81* and *D5S84*, while patient CC's proximal breakpoint is in the same region.

Discussion

We undertook high-resolution cytogenetic and molecular analyses of three patients with interstitial deletions in the *APC* region of the long arm of chromosome 5. The results obtained by these two different approaches are entirely consistent with each other and with the clinical findings for the patients. Three of the markers that were used flank the *APC* gene. C11p11 (*D5S71*) has been physically mapped to 5q21-q22 (Bodmer et al. 1987) and YN5.48 (*D5S81*) to 5q21-q23 (Neuman et al. 1990). *D5S84* is about 5 cM distal to *D5S81* (Nakamura et al. 1988). As we prepared our results for publication, a mutation in sporadic colon cancers was detected in *MCC* from this region of chromosome 5 (Kinzler et al. 1991*b*). *MCC* is approximately 150 kb proximal to the more recently identified *APC* gene (Groden et al. 1991; Joslyn et al. 1991; Kinzler et al. 1991*a*; Nishisho et al. 1991). We synthesized a PCR probe on the basis of the published sequence of *MCC* and examined, by quantitative Southern analysis, patients SD and CC for its loss. The results of the cytogenetic and molecular analyses are summarized in figure 6.

The finding of extensive polyposis in patient EC, whose large deletion spans this region, is exactly what, in light of her age, would be predicted on the basis of either the cytogenetic or the molecular data. However, by using only the cytogenetic analysis in conjunction with the physical map, it is not possible to predict with certainty which of the two boys, if either, is at risk to develop polyposis and colon cancer. When the molecular data are included, predictions can be made. Because *MCC* and, by inference, *APC* are deleted in patient SD, he will quite likely begin to develop polyps within the next 10 years. He will need to be watched closely in the future, so that prophylactic action can be taken. It is not surprising that patient SD has no signs of polyposis at the age of 13 years, since polyps usually do not develop until later in life in affected individuals. Conversely, since the *APC-MCC* region is not deleted in patient CC, he is at low risk for polyposis and need not be monitored for it.

The phenotypic consequences of deletions of this region of chromosome 5 have not been clearly defined. This is, in part, because fewer than 25 patients have been reported, including those with deletions of the most proximal of the three dark G-bands (q14). In addition, the deletions appear to be heterogeneous and have not been well delineated cytogenetically, nor have any of them been studied with molecular markers. However, since the map position of *APC* has been known, a few reports with reliable cytogenetic and phenotypic descriptions have appeared and have recently been compiled by de Michelena et al. (1990). We have tried to clarify the picture further by using their basic format in table 1 but have eliminated those cases with uncertain breakpoints and those involving band q14.

There are now four patients (Herrera et al. 1986; Hockey et al. 1989), including patient SD, whose deletions encompass approximately the region from q15 to q22, and a common phenotype is emerging. These

Figure 3 Results of in situ hybridizations of the probes C11p11 (*A* and *B*) and MC5.61 (*C* and *D*) to the chromosomes 5 of patients SD (*A* and *C*) and CC (*B* and *D*). The bars next to each band on the ideograms indicate the number of grains observed over those bands. For each hybridization, 30–66 cells were scored.

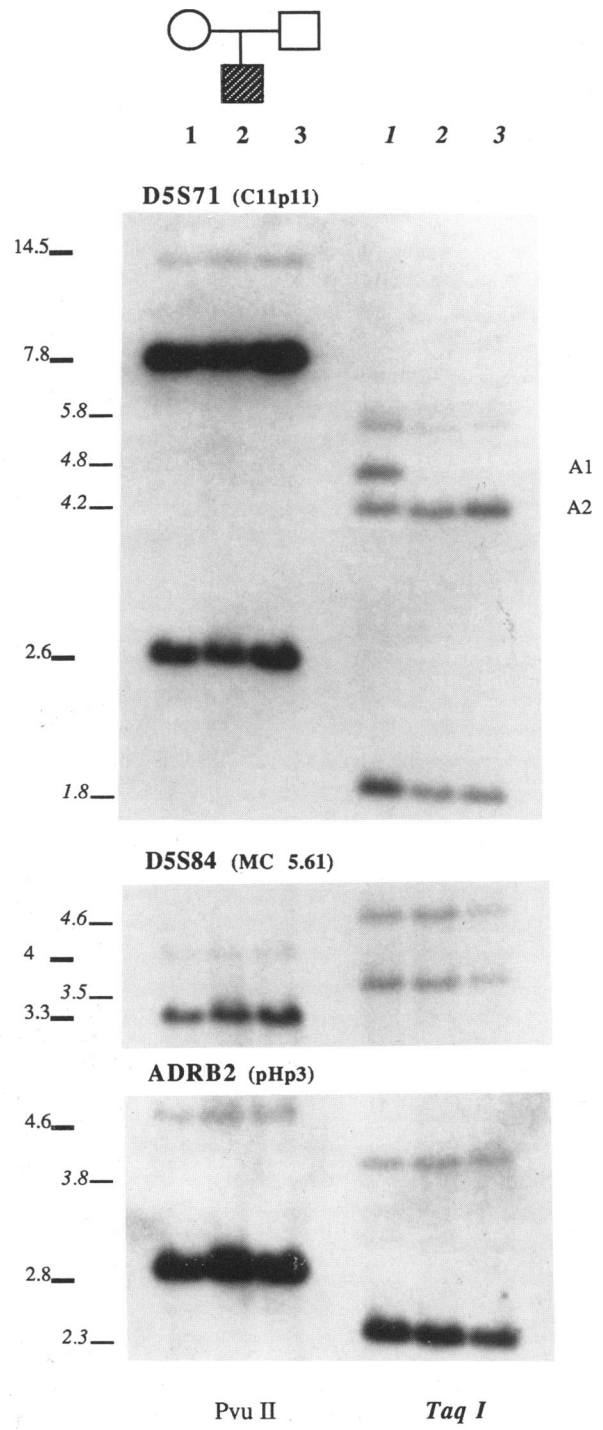


Figure 4 *Pvu*II (*left*) and *Taq*I (*right*), digested DNA from patient SD (lanes 2), from his mother (lanes 1), and from his father (lanes 3) was hybridized successively with three probes on 5q. The heavy loading in lane 2 of the *Pvu*II-digested samples reveals both a strong signal for the MC5.61 and pHp3 probes and a comparatively reduced C11p11 intensity. C11p11 (*D5S71*) recognizes a *Taq*I RFLP for which patient SD's mother (lane *1*) is heterozygous (A1/A2), for which his father (lane *3*) is homozygous (A2/A2), and for which patient SD (lane *2*) is hemizygous (A2). These data are interpreted as indicating deletion of *D5S71* but not of *D5S84*, as the latter signals match the intensity of the *ADRB2* control.

individuals are rather mildly affected, in terms of both mental retardation and physical features, and thus tend to be diagnosed at an older age. Their facial dysmorphism is slight but significant for macrognathia, apparent hypertelorism, and a high forehead. Their characteristics also include a well-demarcated wide philtrum, a high-arched palate, and a carp mouth, which was common to our patient SD and to the brothers reported by Hockey et al. (1989). Deformed limbs and hip dislocation may be present in some patients. It is likely that organ abnormalities, such as horseshoe kidneys, will also be found when they have been looked for specifically. Earlier recognition of these individuals may now be possible and is desirable, since they are at risk for polyposis and colon cancer.

Two patients (Felding and Kristofferson 1980; de Michelena et al. 1990) with deletions of the region from q15 to q31 have been described, and patient CC has a deletion of part of that region. It appears that lack of the distal portion from q22 to q31.1 is responsible for much of the phenotype, as patient CC shares nearly all of the features of the two patients who have deletions that also include the region from q15 to q22.2. These patients are all severely developmentally delayed and have been diagnosed in infancy or early childhood. They are all small and suffered from both failure to thrive and hypotonia in the first months of life. Each has significant facial dysmorphism including hypertelorism, a flat nasal bridge, micrognathia, and abnormal ears. Two of the three have down-slanting palpebral fissures, and all have a short neck. All three have abnormalities of the hip joint (dislocation or contracture), and the anus is displaced anteriorly in two of them. Although the deletions in some children with these characteristics are likely to include *APC* and *MCC*, the development of polyposis may not be observed in most cases, because of early death. At least one of these three children died before the age of 2 years, and the other two have had significant medical difficulties early on.

It is curious that both patient EC and the patient described by de Michelena et al. (1990) had two independent chromosome abnormalities and that band 11q21 was involved in both patients. The additional

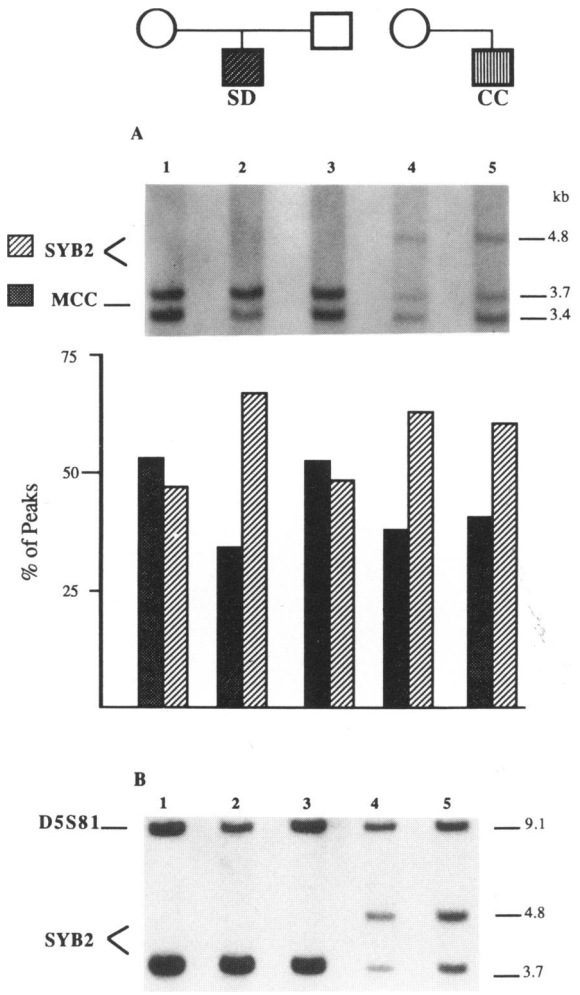


Figure 5 Quantitative Southern analysis of DNA from patients SD and CC and from controls that was digested with *PstI* and that was loaded as indicated by the pedigrees (*top*). *A*, Simultaneous hybridization of *MCC* and *SYB2* probes, which reveals a single 3.4-kb *MCC* fragment (lanes 1–5) and two allelic fragments, 3.7 kb and 4.8 kb, for *SYB2*. Samples in lanes 1–3 are homozygous for the 3.7-kb *SYB2* fragment, and those in lanes 4 and 5 are heterozygous for it. Direct quantitation of the beta emissions from the fragments are presented, as percent of all peaks, below each lane. The relative intensities of *SYB2* signals differ between the homozygous and heterozygous samples. Therefore, lanes 1 and 3 serve as controls for patient SD in lane 2, and lane 4 serves as control for patient CC in lane 5. *B*, Hybridization of the same *PstI* filter with both the *D5S81* probe YN5.48 and the *SYB2* probe reveals a 9.1-kb fragment specific for *D5S81* in all lanes, as well as the same fragment for *SYB2* as seen in *A*. When compared with those in his parents, it is evident that the *MCC* and *D5S81* signals in patient SD are reduced relative to the *SYB2* signals. No difference is seen between patient CC and his mother.

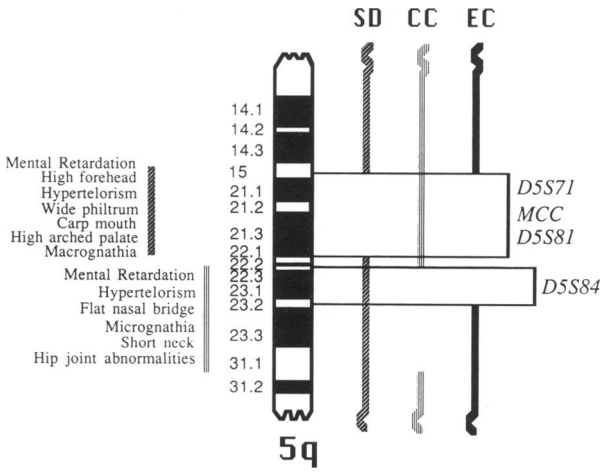


Figure 6 *Left,* Salient phenotypic features of patients SD and CC. *Right,* Regional mapping of *MCC* and flanking loci, on the basis of combined results from Southern blot analysis and in situ hybridization studies. Vertical bars indicate the regions of chromosome 5q present in the three deletion patients.

abnormality in their patient was a translocation, t(1; 11) (p22;q21). Further, patient EC's niece is reported to have a ring chromosome 6. Perhaps these families with multiple anomalies are genetically predisposed to such events, or perhaps they have been exposed to environmental mutagens, but patient EC's family is unaware of any. Although the possibility that these other chromosome abnormalities contribute to the phenotype cannot be completely excluded, this seems unlikely. No loss of material is apparent in either the translocation or the insertion, and deletions would be expected to have an overriding effect.

The experiments reported here provide physical map locations for *MCC* and *D5S84,* which previously were mapped only by linkage analysis (Nakamura et al. 1988; Kinzler et al. 1991*b*). The Southern hybridization results which indicate that patient SD has a deletion of *MCC* provide a physical localization in band 5q21 (fig. 5). The in situ hybridizations of MC5.61 to normal chromosomes 5 indicate a position for *D5S84* at the region from 5q21 to q23. However, because both patient EC's and patient CC's deletions include the sequence, the assignment can be narrowed to the region from q22.3 to q23.2 (fig. 6). The map position of *D5S71* (C11p11) and *D5S81* (YN5.48), derived from these studies, is 5q21 (fig. 6), which is consistent with previously published findings (Bodmer et al. 1987; Neuman et al. 1990).

Table 1

Characteristics of Patients with Deletions of 5q

Characteristic	Case						
	1[a]	2[b]	3[b]	4[c]	5[d]	6[e]	7[f]
Deletion	q15q22	q15q22	q15q22	q15q21.3	q15q31	q15q31	q22.3q31.1
Age at diagnosis	42 years	33 years	31 years	13 years	2 years	1 year	8 mo
Sex	M	M	M	M	F	F	M
Birth weight (g)	. . .	. . .	. . .	3,770	3,460	2,620	2,750
Failure to thrive	. . .	. . .	. . .	−	+	+	+
Short stature	. . .	−	−	−	+	+	+
Hypotonia	−	−	−	−	+	+	+
Mental retardation	+ +	+	+	+	+ +	+ +	+ +
High forehead	−	+	+	+	−	+	+
Hypertelorism	−	±	±	±	+	+	+
Epicanthal folds	−	−	−	−	−	+ +	+ +
Flat nasal bridge	−	−	−	±	+	+	+
Abnormal ears	−	−	−	+	+	+	+
Micrognathia	−	−	−	−	+	+	+
Macrognathia	+	+	+	+	−	−	−
Low hairline	−	−	−	−	+	+	−
Short neck	−	−	−	−	+	+	+
Abnormal kidneys	+	−	−	. . .	+	. . .	. . .
Polyposis	+	+	+	−	−	−	−
Dislocated hips	+	−	−	−	+	+	+
Limb abnormality	+	+	−	−	−	−	+

Note.—Plus sign (+) denotes presence of characteristic; minus sign (−) denotes absence of characteristic; and ellipsis indicates that information was unavailable or unknown.

[a] From Herrera et al. (1986).

[b] From Hockey et al. (1989).

[c] Present patient SD.

[d] From Felding and Kristofferson (1980).

[e] From de Michelena et al. (1990).

[f] Present patient CC.

Acknowledgments

We thank Lisa Gibson for her exceptional technical help, and we thank Gina Williams for her secretarial assistance. This work was supported in part by NIH grant HG00298 (to U.F.) and by the Howard Hughes Medical Institute, of which U.F. is an investigator and T.O. is an associate.

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