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A Gene for Familial Juvenile Polyposis Maps to Chromosome 18q21.1

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Summary

Familial juvenile polyposis (FJP) is a hamartomatous polyposis syndrome in which affected family members develop upper and lower gastrointestinal juvenile polyps and are at increased risk for gastrointestinal cancer. A genetic locus for FJP has not yet been identified by linkage; therefore, the objective of this study was to perform a focused genome screen in a large family segregating FJP. No evidence for linkage was found with markers near *MSH2, MLH1, MCC, APC,* HMPS, *CDKN2A,* JP1, *PTEN, KRAS2, TP53,* or *LKB1*. Linkage to FJP was established with several markers from chromosome 18q21.1. The maximum LOD score was 5.00, with marker *D18S1099* (recombination fraction of .001). Analysis of critical recombinants places the FJP gene in an 11.9-cM interval bounded by *D18S1118* and *D18S487,* a region that also contains the tumor-suppressor genes *DCC* and *DPC4*. These data demonstrate localization of a gene for FJP to chromosome 18q21.1 by linkage, and they raise the possibility that either *DCC* or *DPC4* could be responsible for FJP.

Introduction

Familial juvenile polyposis (FJP) is an autosomal dominant condition characterized by multiple juvenile polyps of the gastrointestinal (GI) tract. Kindreds have been described in which there is involvement of the colon only (juvenile polyposis coli, MIM 174900) (Veale et al. 1966; Grotsky et al. 1982; Rozen and Baratz 1982), the upper GI tract (Watanabe et al. 1979), and both upper and lower GI tracts (generalized polyposis) (Sachatello et al. 1970; Stemper et al. 1975; Jarvinen and Franssila 1984), although whether these are distinct clinical entities is not clear. Affected family members often present with blood per rectum or anemia in the 2d decade of life (Jass et al. 1988). Microscopically, the polyps contain cystically dilated glands, abundant stroma, and an inflammatory infiltrate (Morson 1962). There have been many reports of patients with juvenile polyposis developing gastrointestinal malignancy, including colon cancer (Stemper et al. 1975; Liu et al. 1978; Goodman et al. 1979; Rozen and Baratz 1982; Jarvinen and Franssila 1984; Ramaswamy et al. 1984; Baptist and Sabatini 1985; Jones et al. 1987; Bentley et al. 1989; Scott-Conner et al. 1995), stomach cancer (Stemper et al. 1975; Yoshida et al. 1988; Scott-Conner et al. 1995), and pancreatic cancer (Stemper et al. 1975; Walpole and Cullity 1989). Affected family members' risk of developing GI malignancy has been estimated to be from 9% (Jarvinen and Franssila 1984) to as high as 50% (Jass 1990). Development of adenocarcinoma has been hypothesized to begin with an adenomatous focus within a juvenile polyp, which later becomes dysplastic, and finally undergoes malignant transformation (Goodman et al. 1979; Jarvinen and Franssila 1984).

FJP is a hamartomatous polyposis syndrome, as are Peutz-Jeghers syndrome (PJS) and Cowden disease (CD). Although the polyps in PJS are true hamartomata, some may undergo adenomatous change, and these family members are at increased risk for gastrointestinal malignancy. The PJS gene was mapped to chromosome 19p by comparative genomic hybridization and linkage (Hemminki et al. 1997; Mehenni et al. 1997), and germline mutations were identified in the serine threonine kinase gene *LKB1* (Hemminki et al. 1998). In CD, affected family members may develop multiple hamartomata of the skin, breast, thyroid, oral mucosa, or GI tract, and they are at risk for breast and thyroid malignancies. The gene for CD was localized to chromosome 10q22-23 by linkage (Nelen et al. 1996), and germline mutations in the *PTEN* gene have been found in affected family members (Liaw et al. 1997). A third entity, termed the "hereditary mixed-polyposis syndrome" (HMPS), differs from these syndromes in that affected family members have atypical juvenile polyps, colonic adenomas, and colorectal carcinomas. A gene for HMPS has been mapped to chromosome 6q by linkage (Thomas et

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al. 1996), and it remains uncertain whether HMPS is a distinct clinical syndrome or a variant of FJP (Whitelaw et al. 1997).

Linkage studies in FJP families have been limited, with one report excluding *APC* and *MCC* as the genes for FJP (Leggett et al. 1993). Other genetic studies, originally stimulated by the finding of an interstitial deletion at 10q22-24 in an infant with multiple colonic juvenile polyps and several congenital abnormalities (Jacoby et al. 1997*b*), have focused on the region of the *PTEN* gene. Evaluation for loss of heterozygosity in this region within juvenile polyps revealed somatic deletions within the lamina propria in 39 (83%) of 47 polyps derived from 13 unrelated patients with FJP and 3 patients with sporadic juvenile polyps. These findings have been interpreted as evidence for a tumor-suppressor gene on 10q for FJP (termed "JP1") (Jacoby et al. 1997*a*), but a recent study of 14 FJP families found neither mutations in *PTEN* nor evidence of linkage to markers on 10q22-24 (Marsh et al. 1997). Analysis of an additional 11 cases of FJP also did not uncover mutations in the *PTEN* gene (Riggins et al. 1997). Lynch et al. (1977) reported one family thought to have both juvenile polyposis syndrome and CD as having a nonsense mutation in *PTEN*, and Olschwang et al. (1998) described three patients with juvenile polyposis as having *PTEN* mutations. Whether these four individuals should truly be considered as having juvenile polyposis rather than CD is not clear from these reports. The objective of the present study was to identify by linkage analysis the chromosomal locus of the FJP gene in a large kindred with generalized juvenile polyposis and gastrointestinal cancer.

Patients and Methods

Patients

Informed consent was obtained from family members with the approval of the Institutional Review Board at the University of Iowa. Pathology slides and medical records were reviewed at the University of Iowa to confirm the diagnosis of FJP. Individuals were considered to be affected if they had histologic evidence of upper gastrointestinal or colorectal juvenile polyps. Deceased individuals with a history of gastrointestinal cancer and/or affected offspring were also designated as affected. Living kindred members without a definitive histologic diagnosis of FJP were classified as having unknown affection status.

Genotyping Studies

Peripheral blood was drawn and DNA extracted using a salting-out procedure (Miller et al. 1988). Simple-tandem-repeat polymorphism (STRP) markers were selected from different candidate regions according to the relevant literature, contig maps were obtained from the human physical mapping project at the Whitehead Institute for Biomedical Research/MIT Center for Genome Research (http://www-genome.wi.mit.edu), and genetic maps were obtained from the Center for Medical Genetics (http://www.marshmed.org/genetics). Primers were obtained from Research Genetics and were amplified by PCR in a total volume of 10 μl. PCR reaction conditions included 25 ng of DNA; 200 μM each of dGTP, dATP, dTTP, and dCTP; 1 μl of 10 × buffer (100 mM Tris-HCl, pH 8.3, 500 mM KCl, 15 mM $MgCl_2$, 0.01% w/v gelatin); 2 pmol of each primer; and 0.375 U *Taq* DNA polymerase. Samples were incubated in a thermocycler for 1 min at 94°C, 1 min at 55°C (or optimal annealing temperature), and 1 min at 72°C, for a total of 35 cycles. After amplification, 5 μl of stop solution (95% formamide, 10 mM NaOH, 0.05% bromophenol blue, 0.05% xylene cyanol) was added. Samples were heated to 95°C and were then electrophoresed through 6% denaturing polyacrylamide gels for 2–4 h at 60 W. Gels were silver stained (Bassam et al. 1991), and genotypes were determined from the gels.

Linkage Analysis

Genotype data were entered into a Macintosh computer using a Hypercard-based program (Nichols et al. 1993). Marker data were exported to a DOS-compatible computer, where linkage analysis was performed using the LODSCORE and MLINK subroutines of the FASTLINK (2.3) version (Cottingham et al. 1993) of the LINKAGE program package (Lathrop et al. 1985). Although the gene frequency for FJP is not known, for this study it was estimated to be 1/100,000. This was based on Burt's estimate that FJP is less common than PJS, which is approximately one-tenth as common as familial adenomatous polyposis (which has an incidence of 1 in 8,000) (Burt et al. 1993). Complete dominance of the disease allele (A) was assumed, and penetrance was set at AA = 0.95, Aa = 0.95, and aa = 0.00. For chromosome 18q markers, linkage was also calculated with penetrance values as described for HMPS (AA = 0.95, Aa = 0.95, and aa = .075) (Thomas et al. 1996). No age-specific liability classes were used to further estimate penetrance. Since allele frequencies could not be reliably established in this one kindred with few spouses, initial linkage analyses were performed using equal allele frequencies. For markers from 18q, analyses were performed using equal frequencies as well as those from the CEPH database (http://www.cephgb.fr).

Mapping of DCC

The GeneBridge 4 radiation-hybrid–mapping panel was screened (Walter et al. 1994) using primers from an intragenic DCC dinucleotide repeat (Risinger and Boyd 1992). DCC was placed relative to STSs in the White-

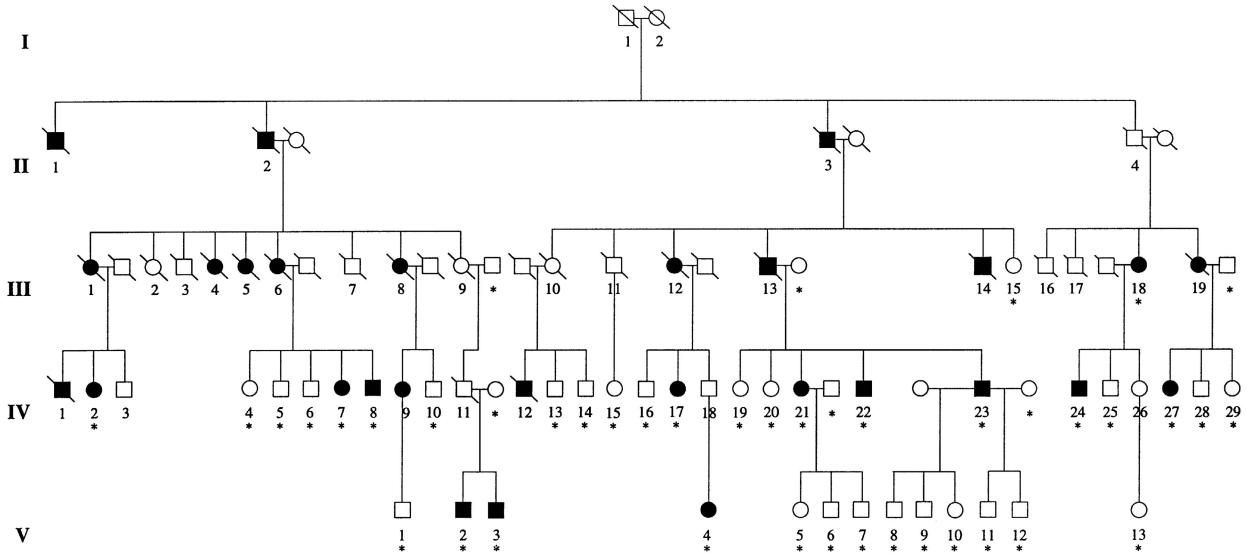

Figure 1 Pedigree of a five-generation American midwestern FJP family (the Iowa FJP kindred). Blackened symbols designate affected family members; unblackened symbols indicate unaffected individuals or those with unknown affection status; genotyping was performed on those marked by asterisks (*).

head Institute for Biomedical Research/MIT Center for Genome Research radiation-hybrid map of the human genome by means of the RHMAPPER server (http://www-genome.wi.mit.edu/cgi-bin/contig/rhmapper.pl).

Results

FJP Kindred

The Iowa FJP kindred was the first FJP kindred described exhibiting a wide variety of gastrointestinal carcinomas (Stemper et al. 1975). The updated pedigree contains 54 living and 24 deceased members (fig. 1). A total of 29 family members have had juvenile polyposis and/or GI cancer, 27 with colorectal, 11 with upper GI, and 9 with both upper- and lower-GI involvement. Eleven individuals have had colon cancer, and 6 have had upper gastrointestinal cancer (4 stomach, 1 duodenum, and 1 pancreas). Five family members have affected offspring but have never been clinically screened for polyps, 4 have had negative endoscopic or radiologic evaluation of the colon after the age of 50 years, and 39 others either have not been screened for polyps or have been screened prior to age 50 years. No family members had a history of thyroid or breast carcinoma or of pigmented macules of the buccal mucosa (Stemper et al. 1975).

Linkage Analysis

Genotyping was performed on 43 individuals, of whom 13 were affected (all with a histologic diagnosis of gastrointestinal juvenile polyps), 24 were considered to be at risk, and 6 were spouses. The linkage strategy involved the typing of markers at loci known to play an important role in colorectal polyposis or cancer. This included the regions of *MSH2* (2p16), *MLH1* (3p21), *MCC*, *APC* (5q21-22), HMPS (6q21), JP1, *PTEN* (10q22-24), *KRAS2* (12p12), *TP53* (17p13), *DCC* (18q21), and *LKB1* (19p). Markers in the region of *CDKN2A* (9q21) were also studied.

Table 1 summarizes the findings of linkage analysis with most of these markers. There was no evidence to suggest linkage to loci predisposing to hereditary nonpolyposis colorectal cancer (*MSH2* and *MLH1*) or familial adenomatous polyposis (*APC*), or to several loci known to play an important role in the genesis of sporadic colorectal cancer (*MCC*, *KRAS2*, and *TP53*). There was also no evidence for linkage to loci involved in other hamartomatous polyposis syndromes, including HMPS, *PTEN*, and *LKB1*. Linkage of FJP to a putative tumor-suppressor gene on 10q22-24 (JP1) was also not suggested by these data.

In contrast, strong evidence for linkage to markers on 18q21.1 was found. The two-point maximum likelihood data for 27 18q markers are summarized in table 2. Seven markers had LOD scores exceeding 3.0, with a maximum LOD (Z_{max}) of 5.00 at *D18S1099* ($\theta = 0.001$). All of these markers have been mapped to the YAC contig WC18.4 (http://www-genome.wi.mit.edu). Five affected individuals had recombination events detected with these 18q21 markers: IV-11 with *D18S548*; IV-7 with *D18S460*, *D18S970*, and *D18S1118*; III-13 with *D18S970* and *D18S1118*; IV-2 with *D18S487*, *D18S858*, *D18S849*, and *D18S1147*; and II-4 with

Table 1

Pairwise LOD Scores for FJP versus Candidate-Region STRPs

	LOD Score at θ =						
STRP	.00	.01	.05	.10	.20	.30	.40
D2S123	−10.41	−3.69	−1.63	−.81	−.18	.02	.06
D2S1352	−26.24	−7.21	−5.46	−1.75	−.56	−.12	.03
D2S1364	−9.02	−1.41	−.10	.31	.45	.33	.15
D3S1611	−15.40	−4.66	−2.07	−1.10	−.37	−.10	.00
D3S1768	−4.15	−1.77	−.43	.02	.24	.18	.06
D5S1453	−26.68	−10.41	−5.23	−3.07	−1.22	−.43	−.10
D5S1467	−14.96	−4.43	−1.83	−.88	−.20	−.03	−.02
D5S346	−7.48	−1.53	−.31	.08	.22	.12	.00
D6S1028	−9.01	−1.26	−.08	.26	.34	.23	.10
D6S283	−7.91	−1.39	.38	.86	.91	.61	.26
D6S301	−8.43	−1.35	−.17	.16	.21	.09	.01
D6S434	−18.77	−3.78	−1.21	−.34	.16	.16	.08
D6S475	−18.98	−6.78	−3.29	−1.87	−.70	−.24	−.06
D9S259	−14.28	−4.55	−1.96	−1.00	−.30	−.07	−.01
D9S304	−14.15	−4.36	−2.00	−1.01	−.22	.03	.07
D9S319	−13.91	−4.46	−1.53	−.34	.51	.63	.41
D10S1242	−17.49	−6.51	−3.08	−1.72	−.59	−.17	−.03
D10S1427	−3.53	.45	.93	.95	.71	.42	.17
D10S219	−5.44	−1.55	−.32	.12	.39	.35	.19
D10S1753	−5.04	−.72	.42	.71	.68	.42	.14
D10S573	−9.77	−5.29	−2.49	−1.36	−.43	−.11	−.02
D12S372	−9.68	−3.52	−1.54	−.79	−.22	−.04	.01
D12S389	−9.71	−4.94	−2.25	−1.21	−.40	−.12	−.03
D17S922	−9.04	−1.72	−.53	−.17	.02	.03	.01
D17S953	−9.63	−3.94	−1.67	−.76	−.09	.09	.08
D17S960	−9.97	−2.18	−.78	−.28	.01	.04	.02
D17S969	−9.45	−2.45	−.61	−.03	.26	.23	.12
D19S565	−24.77	−9.27	−4.61	−2.77	−1.17	−.49	−.20
D19S886	−3.57	−1.36	−.16	.19	.29	.18	.05
D19S894	−7.20	−.82	.93	1.39	1.36	.95	.45

D18S862 and *D18S1147*. Analysis of these critical recombinants places the FJP gene between *D18S1118* and *D18S487* (fig. 2), an interval of ~11.9 cM and 34 cR (Center for Medical Genetics, Whitehead Institute for Biomedical Research/MIT Center for Genome Research). The *DCC* gene was placed within this interval by means of the GeneBridge 4 radiation-hybrid panel (Walter et al. 1994), between *WI-5257* and *WI-4115*.

Linkage analysis was performed under several different assumptions, without changing the overall results. First, clinically unaffected individuals were scored as unknown, with a penetrance of 95% for genotype AA, 95% for Aa, and 0% for aa. Next, four individuals >50 years of age, with negative colonoscopy or barium enema results, were classified as unaffected, and the same penetrance values were used as described for HMPS (AA = 95%, Aa = 95%, aa = 7.5%) (Thomas et al. 1996). LOD scores of >3.0 were found with the same seven markers (*D18S474*, *D18S1099*, *D18S46*, *D18S363*, *DCC*, *D18S484*, and *D18S858*) with both assumptions, using the allele frequencies in the CEPH database (http://www.cephgb.fr), without significant differences in recombination fraction (θ). Linkage analysis was also performed using equal allele frequencies, which resulted in LOD scores of >3.0 with 10 different markers (*D18S470*, *D18S1110*, *D18S474*, *D18S1099*, *D18S46*, *D18S363*, *DCC*, *D18S484*, *D18S846*, and *D18S977*). The data reported in table 2 were derived by means of the first method described, which appeared to use the most conservative assumptions for linkage analysis. Linkage analysis was also performed by classifying deceased individuals with a history of GI cancer and/or affected offspring (but without histologic confirmation of juvenile polyposis) as having unknown affection status, which did not change these results.

Discussion

FJP is the last of the hamartomatous polyposis syndromes to be localized by genetic linkage analysis. The focused genome screen used here identified a locus on chromosome 18q21.1, which is at variance with the previous suggestion of a tumor-suppressor gene (JP1) for FJP on 10q22-24 (Jacoby et al. 1997*a*). There was no evidence of linkage to the 10q markers used here, which spanned the 10q22-24 region containing the *PTEN* gene. It is worth noting that identification of JP1 was based on loss-of-heterozygosity studies and not on genetic linkage. Jacoby et al. (1997*a*) found deletion of

Table 2

Pairwise Linkage Results of FJP versus Chromosome 18 STRPs

STRP	θ	Z_{max}
D18S978	.140	.84
D18S548	.080	1.03
D18S460	.157	.37
D18S970	.500	.00
D18S1118	.152	.57
D18S473	.001	2.14
D18S470	.001	2.59
D18S1110	.001	2.47
D18S474	.001	4.24
D18S1099	.001	5.00
D18S46	.001	4.41
D18S363	.001	4.46
DCC	.001	4.79
GATA06	.001	2.36
D18S1156	.001	1.37
D18S851	.016	1.60
D18S484	.025	3.31
D18S539	.013	2.10
D18S487	.111	1.22
D18S69	.065	1.42
D18S846	.001	1.46
D18S858	.048	3.20
D18S977	.001	2.69
D18S849	.105	2.58
D18S862	.229	.32
D18S1147	.174	1.51
D18S979	.420	.03

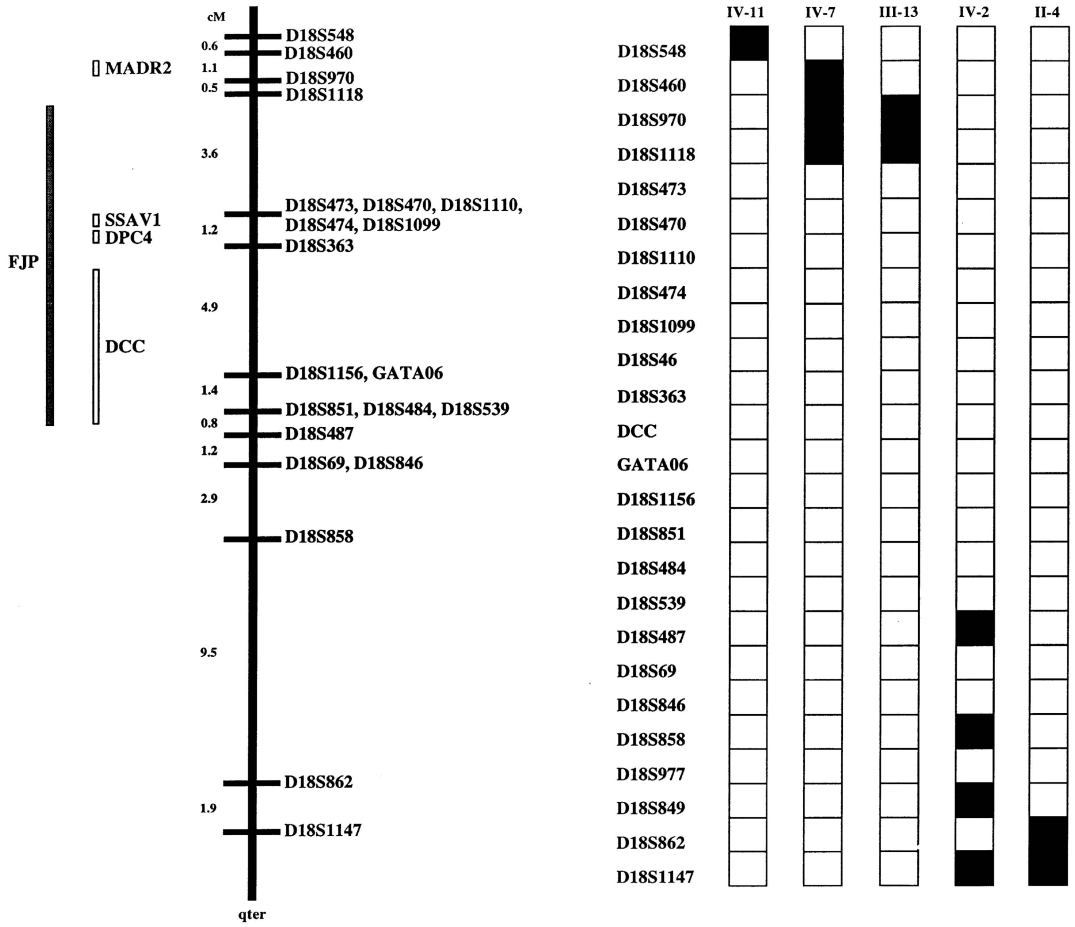

Figure 2 Schematic representation of STRPs and genes from 18q21 (*left*) and recombination analysis of key affected individuals (*right*). STRPs are listed in their map order, based on the Center for Medical Genetics map; markers *D18S977* and *D18S849* lie between *D18S858* and *D18S862* (Whitehead Institute for Biomedical Research/MIT Center for Genome Research); and *D18S46* lies between *DPC4* and *D18S363* (Hahn et al. 1996*a*). The locations of *MADR2*, *SSAV1*, *DPC4*, and *DCC* are representations derived from physical mapping data (Eppert et al. 1996); the lengths of the corresponding bars shown for the map at left do not necessarily reflect the size of each gene. To the right, informative recombination events in affected individuals that define the interval of the FJP gene are depicted as blackened boxes; unblackened boxes designate noninformative meioses. These data suggest that the FJP gene lies between the markers *D18S1118* and *D18S487*.

one allele of *D10S219* in 39 (83%) of 47 juvenile polyps, and fluorescent in situ hybridization demonstrated that 10q deletions occurred within the lymphocytes and macrophages of the lamina propria, but not in epithelial cells. These results supported the theory that overgrowth of the lamina propria is the determining event in juvenile polyp formation (Jass 1990). Recent reports that four individuals with juvenile polyposis had *PTEN* germline mutations would appear to confirm that *PTEN* is the predisposing gene on 10q22-24 in some families with juvenile polyposis (Lynch et al. 1997; Olschwang et al. 1998). However, one of these patients was described as having both CD and juvenile polyposis (Lynch et al. 1997), whereas the other three had no family history of juvenile polyposis (and one of these had a thyroid nodule) (Olschwang et al. 1998). These reports raise the question whether these patients were truly affected with juvenile polyposis or CD (Eng and Ji 1998 [in this issue]). In 14 FJP families, Marsh et al. (1997) found no evidence of linkage to markers on 10q22-24 or mutations in the *PTEN* gene, which they concluded ruled out *PTEN* or another gene in this region as the locus for FJP, at least in a subset of these families. Similar results were found by Riggins et al. (1997) and are in agreement with the findings of the present study, which would rule out germline mutations on 10q22-24 as the predisposing event leading to FJP in this large family. It is likely that there is genetic heterogeneity for the juvenile polyposis syndromes, and perhaps mutations at HMPS and *PTEN* represent the changes seen in some families, whereas a locus for generalized polyposis predisposing to gastrointestinal carcinoma resides on 18q21.1. The findings of

this study should help to establish FJP as a distinct entity rather than a variant of one of the other hamartomatous polyposis syndromes, such as PJS on 19p13 or CD on 10q23. Genetic methods will ultimately prove to be more useful for the classification of different families with hamartomatous polyposis than current methods based on clinical phenotype.

Analysis of critical recombinants places the FJP gene in an 11.9-cM interval between the markers *D18S1118* and *D18S487* (Center for Medical Genetics). Linkage analysis revealed no recombinants with the markers *D18S473, D18S470, D18S1110*, *D18S474*, *D18S1099*, *D18S46*, *D18S363*, *DCC*, *GATA06*, *D18S1156*, *D18S846*, or *D18S977* (the latter two markers being telomeric to the interval defined by critical recombinants). The finding of genetic linkage with markers on 18q21.1 makes presymptomatic testing of at-risk individuals in this family possible. This would allow those who have not inherited the affected parental allele to potentially be spared from repetitive endoscopic screening for GI neoplasms, whereas those predicted to be gene carriers would benefit from close surveillance for the development of these tumors. Although prophylactic surgery has been proposed (Scott-Conner et al. 1995), this may not be necessary if periodic screening and endoscopic polypectomy are carried out.

One candidate gene from 18q21.1 that can be excluded from consideration as the FJP gene is *MADR2*, which has been physically mapped to between *D18S460* and *D18S970* (Eppert et al. 1996), centromeric to the recombination events seen in individuals III-13 and IV-7. This interval on 18q21.1 does contain *DCC*, a tumor-suppressor gene lost in many sporadic colorectal carcinomas (Vogelstein et al. 1988; Fearon et al. 1990). *DCC* spans ~1.4 Mb in genomic DNA (Cho et al. 1994) and has been shown to encode for a netrin receptor (Keino-Masu et al. 1996). Its role in the genesis of colorectal carcinoma is uncertain, since transgenic mice lacking a functional *DCC* gene manifest not an increased rate of intestinal tumors, but rather defects in commissural axon projections (Fazeli et al. 1997). The latter study concluded that the loss of *DCC* expression commonly seen in colorectal and pancreatic cancers may be related to changes in a linked gene. The simian sarcoma–associated virus-1 gene (*SSAV1*) also lies within this interval (Eppert et al. 1996) and contains sequences resembling retrovirus long-terminal repeats (Brack-Werner et al. 1989). Also mapping to this region is *DPC4*, a member of the *Mad* gene family, involved in signal transduction of serine threonine kinase receptors (Hahn et al. 1996b). Interestingly, the gene for PJS has just been found to be caused by mutations in the serine threonine kinase gene *LKB1* (Hemminki et al. 1998). *DPC4* is homozygously deleted in ~30% of pancreatic carcinomas, and gene mutations are seen in 22% of pancreatic tumors without homozygous deletions (Hahn et al. 1996*b*). *DPC4* was also found to be lost or altered in 5 (28%) of 18 colorectal carcinoma cell lines (Thiagalingam et al. 1996). The latter study defined the minimally lost region in 55 colorectal carcinoma cell lines to span the 16-cM interval between *D18S535* and *D18S858*, which contains both the *DCC* and *DPC4* genes. This is roughly the same interval to which the FJP gene has been mapped in this study, except that this interval begins 4 cM telomeric to *D18S535* and ends 4 cm centromeric to *D18S858* (Center for Medical Genetics). These results suggest that the gene responsible for FJP could be the same gene on 18q21 that is involved in the development of sporadic colorectal or pancreatic carcinomas; whether this gene will prove to be *DCC* or *DPC4* awaits direct mutational testing in FJP family members.

Acknowledgments

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References

Baptist SJ, Sabatini MT (1985) Coexisting juvenile polyps and tubulovillous adenoma of colon with carcinoma in situ: report of a case. Hum Pathol 16:1061–1063

Bassam BJ, Caetano-Anolles G, Gresshoff P (1991) Fast and sensitive silver staining of DNA in polyacrylamide gels. Anal Biochem 196:80–83

Bentley E, Chandrasoma P, Radin R, Cohen H (1989) Generalized juvenile polyposis with carcinoma. Am J Gastroenterol 84:1456–1459

Brack-Werner R, Barton DE, Werner T, Foellmer BE, Leib-Mosch C, Francke U, Erfle V, et al (1989) Human SSAV-related endogenous retroviral element: LTR-like sequence and chromosomal localization to 18q21. Genomics 4:68–75

Burt RW, Bishop DT, Lynch HT, Rozen P, Winawer SJ (1990) Risk and surveillance of individuals with heritable factors for colorectal cancer. Bull World Health Organ 68:655–665

Cho KR, Oliner JD, Simons JW, Hedrick L, Fearon ER, Preisinger AC, Hedge P, et al (1994) The DCC gene: structural analysis and mutations in colorectal carcinomas. Genomics 19:525–531

Cottingham RW, Idury RM, Schaffer AA (1993) Faster sequential linkage computations. Am J Hum Genet 53: 252–263

Eng C, Ji HL (1998) Molecular classification of the inherited hamartoma polyposis syndromes: clearing the muddied waters. Am J Hum Genet 62:1020–1022 (in this issue)

Eppert K, Scherer SW, Ozcelik H, Pirone R, Hoodless P, Kim H, Tsui L-C, et al (1996) MADR2 maps to 18q21 and encodes a TGFβ-regulated MAD-related protein that is functionally mutated in colorectal carcinoma. Cell 86:543–552

Fazeli A, Dickinson SL, Hermiston ML, Tighe RV, Steen RG, Small CG, Stoeckli ET, et al (1997) Phenotype of mice lacking functional Deleted in colorectal cancer (DCC) gene. Nature 386:796–804

Fearon ER, Cho KR, Nigro JM, Kern SE, Simons JW, Ruppert JM, Hamilton SR, et al (1990) Identification of a chromosome 18q gene that is altered in colorectal cancers. Science 247:49–56

Goodman ZD, Yardley JH, Milligan FD (1979) Pathogenesis of colonic polyps in multiple juvenile polyposis. Cancer 43: 1906–1913

Grotsky HW, Rickert RR, Smith WD, Newsome JF (1982) Familial juvenile polyposis coli: a clinical and pathologic study of a large kindred. Gastroenterology 82:494–501

Hahn SA, Shamsul Hoque ATM, Moskaluk CA, da Costa LT, Scutte M, Rozenblum E, Seymour AB, et al (1996*a*) Homozygous deletion map at 18q21.1 in pancreatic cancer. Cancer Res 56:490–494

Hahn SA, Shutte M, Shamsul Hoque ATM, Moskaluk CA, da Costa LT, Rozenblum E, Weinstein CL, et al (1996*b*) DPC4, a candidate tumor suppressor gene at human chromosome 18q21.1. Science 271:350–353

Hemminki A, Markie D, Tomlinson I, Avizienyte E, Roth S, Loukola A, Bignell G, et al (1998) A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. Nature 391: 184–187

Hemminki A, Tomlinson I, Markie D, Jarvinen H, Sistonen P, Bjorkqvist AM, Knuutila S, et al (1997) Localization of a susceptibility locus for Peutz-Jeghers syndrome to 19p using comparative genomic hybridization and targeted linkage analysis. Nat Genet 15:87–90

Jacoby RF, Schlack S, Cole CE, Skarbek M, Harris C, Meisner LF (1997*a*) A juvenile polyposis tumor suppressor locus at 10q22 is deleted from nonepithelial cells in the lamina propria. Gastroenterology 112:1398–1403

Jacoby RF, Schlack S, Sekhon G, Laxova R (1997*b*) Del (10) (q22.3q24.1) associated with juvenile polyposis. Am J Med Genet 70:361–364

Jarvinen HJ, Franssila KO (1984) Familial juvenile polyposis coli: increased risk of colorectal cancer. Gut 25:792–800

Jass JR, Williams CB, Bussey HJR, Morson BC (1988) Juvenile polyposis—a precancerous condition. Histopathology 13: 619–630

Jass JR (1990) Pathology of polyposis syndromes with special reference to juvenile polyposis. In: Utsunomiya J, Lynch HT (eds) Hereditary colorectal cancer. Springer, Tokyo, pp 343–350

Jones MA, Hebert JC, Trainer TD (1987) Juvenile polyp with intramucosal carcinoma. Arch Pathol Lab Med 111: 200–201

Keino-Masu K, Masu M, Hinck L, Leonardo ED, Chan SS-Y, Culotti JG, Tessier-Lavigne M (1996) Deleted in colorectal cancer (DCC) encodes a netrin receptor. Cell 87:175–185

Lathrop GM, Lalouel J-M, Julier C, Ott J (1985) Multilocus linkage analysis in humans: detection of linkage and estimation of recombination. Am J Hum Genet 37:482–498

Leggett BA, Thomas LR, Knight N, Healey S, Chenevix-Trench G, Searle J (1993) Exclusion of APC and MCC as the gene defect in one family with familial juvenile polyposis. Gastroenterology 105:1313–1316

Liaw D, Marsh DL, Li J, Dahia PLM, Wang SI, Zheng Z, Bose S, et al (1997) Germline mutations of the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome. Nat Genet 16:64–67

Liu T-H, Chen M-C, Tseng H-C (1978) Malignant change of juvenile polyp of colon. Chin Med J (Engl) 4:434–439

Lynch ED, Ostermeyer EA, Lee MK, Arena JF, Ji H, Dann J, et al (1997) Inherited mutations in PTEN that are associated with breast cancer, Cowden disease, and juvenile polyposis. Am J Hum Genet 61:1254–1260

Marsh DJ, Roth S, Lunetta KL, Hemminki A, Dahia PLM, Sistonen P, Zheng Z, et al (1997) Exclusion of PTEN and 10q22-24 as the susceptibility locus for juvenile polyposis syndrome. Cancer Res 57:5017–5021

Mehenni H, Blouin J-L, Radhakrishna U, Bhardwaj SS, Bhardwaj K, Dixit VB, Richards KF, et al (1997) Peutz-Jeghers syndrome: confirmation of linkage to chromosome 19p13.3 and identification of a potential second locus, on 19q13.4. Am J Hum Genet 61:1327–1334

Miller SA, Dykes DD, Polesky HF (1988) A simple salting out procedure for extracting DNA from nucleated cells. Nucleic Acids Res 16:1215

Morson BC (1962) Some peculiarities in the histology of intestinal polyps. Dis Colon Rectum 5:337–344

Nelen MR, Padberg GW, Peeters EAJ, Lin AY, van den Helm B, Frants RR, Coulon V, et al (1996) Localization of the gene for Cowden disease to chromosome 10q22-23. Nat Genet 13:114–116

Nichols BE, Sheffield VC, Stone EM (1993) A user-friendly Hypercard interface for human linkage analysis. Comput Appl Biosci 9:757–759

Olschwang S, Serova-Sinilnikova OM, Lenoir GM, Thomas G (1998) PTEN germ-line mutations in juvenile polyposis coli. Nat Genet 18:12–14

Ramaswamy G, Elhosseiny AA, Tchertkoff V (1984) Juvenile polyposis of the colon with atypical adenomatous changes and carcinoma in situ. Dis Colon Rectum 27:393–398

Riggins GJ, Hamilton SR, Kinzler KW, Vogelstein B (1997) Normal PTEN gene in juvenile polyposis. NOGO 1:1 (http://pathology.jhu.edu/nogo/)

Risinger JI, Boyd J (1992) Dinucleotide polymorphism in the human DCC gene at chromosome 18q21. Hum Mol Genet 1:657

Rozen P, Baratz M (1982) Familial juvenile colonic polyposis with associated colon cancer. Cancer 49:1500–1503

Sachatello CR, Pickren JW, Grace JT (1970) Generalized juvenile gastrointestinal polyposis. Gastroenterology 58: 699–708

Scott-Conner CEH, Hausmann M, Hall TJ, Skelton DS, Anglin BL, Subramony C (1995) Familial juvenile polyposis: patterns of recurrence and implications for surgical management. J Am Coll Surg 181:407–413

Stemper TJ, Kent TH, Summers RW (1975) Juvenile polyposis and gastrointestinal carcinoma. Ann Intern Med 83: 639–646

Thiagalingam S, Lebauer C, Leach FS, Schutte M, Hahn SA, Overhauser J, Willson SA, et al (1996) Evaluation of candidate tumour suppressor genes on chromosome 18 in colorectal cancers. Nat Genet 13:343–346

Thomas HJW, Whitelaw SC, Cottrell SE, Murday VA, Tom-

linson IPM, Markie D, Jones T, et al (1996) Genetic mapping of the hereditary mixed polyposis syndrome to chromosome 6q. Am J Hum Genet 58:770–776

Veale AMO, McColl I, Bussey HJR, Morson BC (1966) Juvenile polyposis coli. J Med Genet 3:5–16

Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, Nakamura Y, et al (1988) Genetic alterations during colorectal tumor development. N Engl J Med 319:525–532

Walpole IR, Cullity G (1989) Juvenile polyposis: a case with early presentation and death attributable to adenocarcinoma of the pancreas. Am J Med Genet 32:1–8

Walter M, Spillett W, Thomas P, Weissenbach J, Goodfellow P (1994) A method for constructing radiation hybrid maps of whole genomes. Nat Genet 7:22–28

Watanabe A, Nagashima H, Motoi M, Ogawa K (1979) Familial juvenile polyposis of the stomach. Gastroenterology 77:148–151

Whitelaw SC, Murday VA, Tomlinson IPM, Thomas HJW, Cottrell SE, Ginsberg A, Bukofzer S, et al (1997) Clinical and molecular features of the hereditary mixed polyposis syndrome. Gastroenterology 112:327–334

Yoshida T, Haraguchi Y, Tanaka A, Higa A, Daimon Y, Mizuta Y, Tamaki M, et al (1988) A case of generalized juvenile gastrointestinal polyposis associated with gastric carcinoma. Endoscopy 20:33–35