Reviewer's report

Title: Age and manifestation related symptoms in familial adenomatous polyposis (FAP)

Version: 4 Date: 12 October 2004

Reviewer: Waltraut Friedl

Reviewer's report:

General

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

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Croner et al. have revised their manuscript on clinical symptoms of 143 FAP patients who had been treated at their hospital between 1971 and 2000. The authors have included most of the referee’s suggestions in their revised manuscript. There remained some minor questions or suggestions:

1. Page 2, abstract, last sentence: FOR patients which present...
2. Page 4, patient population:
   Question 1: were only patients with >100 polyps (according to the definition) included? Does this apply to all the 143 patients? If yes, there should be no group of patients with 10-100 polyps (in table 1, and page 7: 63% had >100 polyps in the colon). Obviously most patients have polyps in the colon and in the rectum, thus making together >100 polyps?
   Question 2: is it possible to have patients registered with FAP in whom even sex is not known? Were these patients excluded from further evaluation, as no other valuable information was obtained on them?
   Question 3: are the 157 (143) patients unrelated? If not, the number of families should also be indicated.
3. Page 5, paragr. 2: The authors replied: “In most cases patients COULD GIVE NO INFORMATION about their family history of cancer related diseases. 18% of our patients were able to give some information about their family history. We revised the manuscript concerning this matter.” These would mean that information on family history of FAP is known only in 18% of 143 = 26 patients. It is not known whether the remaining 117 patients have a family history or not. However, in the revised manuscript the authors wrote: “In twenty-nine of these patients a previously unknown family history of FAP became obvious during clinical diagnostics while the main group of 114 patients had no family members with known FAP”. In the light of the author’s reply his statement is not correct: please indicate on how many patients there is information on family history (perhaps 26? 29? or more?) and how many of the patients with known information belong to “familial” cases.
4. Page 6 (and throughout the manuscript): table 3 and 4 should be replaced by table 1 and 2, respectively.
5. Page 6, Results, paragr. 1: The authors wrote: The diagnosis of FAP was VERIFIED in 43% (9/21 of patients <20 years, 28% (21/76) of patients between 20-40 years and 26% (12/46) of patients >40 years of age by molecular diagnostics”. Comment: it is useless to give the percentage of molecular “verification of diagnosis” in the different age groups. This does not reflect the real mutation detection rate, but rather an accidental figure, especially as patients diagnosed since 1970 were included in this evaluation. If the authors intend to
present and discuss molecular data and the benefit of molecular testing (especially for family members), I would suggest to introduce a special section at the end of the chapter “results”.

6. Page 6, Results, paragr. 2: The sentence is not complete.

7. Page 7, end of paragr. “colorectal manifestations”: here it would be of interest to show how many patients (overall) had CRC at diagnosis when the diagnosis occurred based on symptoms (e.g. bleeding or other bowel symptoms) compared to those patients who had cancer at time of diagnosis but were diagnosed without such symptoms.

8. Page 7/8, extracolonic manifestations: all the data (%) are related to the patient sample of 143 patients. Was this information available for all the patients? If not, please state, e.g.: ...Information on presence or absence of desmoid tumors, gastric gland polyps, duodenal polyps and small bowel polyps was available in xy, xz, nn and nn of patients, respectively. Then the percentage can be calculated for the different manifestations and patient groups.

9. Page 9, last paragr. of “general symptoms”: ...no abdominal pain”.. in 108/143 patients (but on page 8: “abdominal pain in 21/143 patients”. What about the remaining 14 patients? (when no information regarding this item, then reference should be made to 129 patients! The same applies to the other items, please verify and correct, otherwise percentage does not make sense! In this paragraph, it might be of interest, how many patients had NONE of the “general symptoms”.

10. Page 9/10, Bleeding associated with different clinical symptoms: The calculation of percentage of patients with fecal occult blood or bleeding “ASSOCIATED with gastric polyps” (or duodenal polyps or small bowel polyps, etc.) does not make sense, as most of these patients had also colonic polyps (by definition!) or cancer that is likely to be the source of bleeding (the authors state: 90% of patients with >100 polyps have rectal bleeding). The patient groups defined by these symptoms are overlapping and not exclusively, thus, the real cause of bleeding cannot be known. The same applies to “diarrhea”: overall 45/143 patients were found with diarrhea, of them 44 had >100 polyps! Thus, the association with polyps of the small bowel, etc. does not make sense!

11. Page 10, discussion: “...This explains the low detection rate of patients (2%) with FAP by molecular diagnostics in our study. Nevertheless the diagnosis of FAP was verified by molecular diagnostics in 29% of all patients which is available for routine clinical use since the nineties....” The “detection rate of 2%” is not explained in results. Are these “patients detected presymptomatically” by molecular diagnostics? How does this figure fit to the 29%?

12. Page 12, last paragraph: “...In all age groups genetic testing is indispensable TO CLARIFY THE CLINICAL DIAGNOSIS. The offspring of patients with positive tests must be examined and monitored by clinical registers....” This is not correct (there is no need to clarify a clear clinical diagnosis): better: ...In patients of all age groups genetic testing should be recommended in order to allow presymptomatic testing in their sibs and offspring. Family members with positive tests and all persons at risk from families where the mutation could not be identified must be examined and monitored by clinical registers.

What next?: Accept after minor essential revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No
Declaration of competing interests:

None