Reviewer's report

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

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Reviewer: Waltraut Friedl

Reviewer's report:

General
Croner et al. have evaluated clinical symptoms of 143 FAP patients who had been treated at their hospital between 1971 and 2000. The authors present a large cohort of patients who are clinically well characterised and therefore would allow to answer different important questions especially with respect to the clinical course of the disease in untreated patients.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
1. The many data should be presented more clearly. Patients are separated in many groups based on age at diagnosis, and the description of the many proportions of different symptoms in the different age groups is somewhat confusing and difficult to follow.
2. Since the period evaluated covers up to 30 years (1971-2000) the authors find that most patients (120/143) were diagnosed because of symptoms; this large number of symptomatically diagnosed patients may be due to the fact that physicians were not aware - in the first half of the period – of the importance of presymptomatic surveillance in children of FAP patients. It would be interesting to examine whether the proportion of patients diagnosed on symptoms decreases in familial cases during the last years.

There are some surprising results and statements in the manuscript:
3. The authors find only 20% (29/143) patients to have a family history of FAP. This low number contrasts with generally accepted data of about 25% of FAP cases occurring as new mutations. The authors should comment on this discrepancy.
4. The authors state that only 3/143 of the patients were diagnosed by molecular diagnostics (page 79) and discuss the missing FAP register as a reason for the lack of molecular screening and clinical surveillance (page 11). This statement should be presented more clearly: to my knowledge in Erlangen molecular diagnostics has been performed at the Human Genetic department for several years, and in Germany FAP patients and their relatives are offered surveillance and molecular genetic tests even outside of FAP registers. The situation presented might be true before 1990, but not between 1995-2000.
5. In the last paragraph (page 13) the authors state that "in all age groups genetic testing is indispensable to verify the clinical diagnosis". This is not correct: The diagnosis of FAP in its typical form is a clinical diagnosis. If a patient has >100 colorectal adenomas (at a young age) there is no need to verify the clear clinical diagnosis by molecular genetic tests. In case of typical FAP the detection of an APC germline mutation would just confirm the diagnosis. But – more important – detection of an APC germline mutation in FAP patients would allow predictive testing in persons at risk of his family. However, it should be kept in mind that the diagnosis of FAP (and the probability of 50% to pass on the disease to the offspring) cannot be excluded in a patient when no APC mutation is detected.

Some suggestions and questions:
6. The authors have collected valuable clinical information on a large FAP patient group. The data (indirectly and in a very complicated way) reflect the actual knowledge of two different phenotypes: typical FAP (with early onset and >100 adenomas and more distal location) and attenuated FAP (with <100 adenomas, late onset and more proximal location of adenomas). It might be interesting to
evaluate the different clinical symptoms including risk of colorectal cancer, other GI involvement, etc.

7. Of the 5 patients with diagnosis <10y only one had symptoms. What was the basis for diagnosis in the other 4 patients (obviously no symptoms, see tables 1 and 2; was it family history and surveillance?)

8. Is it correct to recommend rectoscopy in patients aged 21-40y (when presenting with bleeding!), and colonoscopy for patients at age >41 y?

9. I would suggest the authors should contact the colleagues from the Department of Human Genetics of their University (who - to my knowledge - are experts in APC diagnostics and problems related to this) and discuss the manuscript with them.

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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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Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

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

Quality of written English: Needs some language corrections before being published

Statistical review: No

Declaration of competing interests: None