Reviewer’s report

Title: The genetic basis of colonic adenomatous polyposis syndromes

Version: 0 Date: 01 Jun 2016

Reviewer: Andy Latchford

Reviewer's report:

The categorisation of adenomatous polyposis syndromes is becoming more complex, with the discovery of new genes. It is important for clinicians to understand the genetic diversity of the adenomatous polyposis syndromes, with their different inheritance patterns and variable clinical features.

General comment:

I do not find this article the easiest to follow. Part of this is because terms are introduced that may exist in OMIM but which are not used clinically ie FAP1, 2 and 3 - these are not helpful terms. One example of why they are not helpful is highlighted in the introduction which states that FAP is an autosomal dominant condition (line 4) but later the author describes FAP 2 and 3 as being recessively inherited. This just creates confusion. I think that the title of the article should be modified to "the genetic basis of adenomatous polyposis syndromes" and the manuscript redrafted accordingly. The terms FAP1, 2, 3 should be dropped and a description of the genetic causes of adenomatous polyposis syndromes described individually. Classifying the adenomatous polyposis syndromes as FAP (for those with an APC mutation), MAP, NAP, PPAP and unclassified would be provide a much clearer manuscript.

Terminology needs to be clear and consistent throughout. Define classical and attenuated FAP (needs an age not just a polyp number eg a 15 year old with 80 adenomas is very different to a 50 year old with 80 adenomas; many would use <100 adenomas at >/=25 years). Explain what is meant by "polyposis". When the term "FAP" is used be clear as to whether you mean a clinical diagnosis, genetic diagnosis or an adenomatous polyposis syndrome etc etc -t appears currently that these are used some interchangeably.

There are a number of language and grammatical errors throughout which need correcting.

Specific comments:

ABSTRACT:
1. I would rewrite this given the comments above. As FAP 1, 2, 3 are not used clinically, the first reading of the abstract makes little sense. What is termed "FAP" in the abstract really is "adenomatous polyposis syndromes", with the different genetic causes and differing inheritance patterns and clinical manifestations. I think the abstract should make this clear.

2. I am not sure that the first sentence makes sense..."the association of germline mutations...with the molecular diagnosis". Should it be clinical diagnosis rather than molecular diagnosis??

3. Line 3 poor grammar - "it was early established"

4. Last line missing an "e" at the end of therefore.

REVIEW OF FAP:

1. As in my general comments please be clear about terms "FAP", "polyposis" etc. It would be helpful not to insert the term attenuated FAP in line 5 unless it is prefaced with a clinical definition of classical and attenuated FAP.

2. I do not understand why the concept of MSI is introduced here. This is very confusing. A solitary reference describing MSI analysis in a cohort of patients with "FAP" is used. In the reference quoted, MSI was rare. Indeed the patients cohort were not a genetic diagnosis of FAP (ie proven germline mutations in APC), rather patients with >100 adenomas. The reason this is important is that well documented that biallelic MUTYH mutations can cause somatic mismatch repair deficiency and therefore MSI-H cancers. This has not been described in patients with a proven APC germline mutation.

CLASSIC FAP:

1. What is meant by "classic" FAP - is this purely a phenotypic description or is the author meaning those with a germline APC mutation who have >100 colonic adenomas?

2. What is meant by the "average age of disease onset"?? Is the author trying to describe the age at which one my expect colorectal cancer to arise, if no intervention is performed?

3. In the extra-colonic manifestations of the disease, please be clear what is meant by "small bowel" when describing cancers. Duodenal ampullary cancers are an important cause of morbidity and mortality. Jejunal and ileal cancers are rare and not really a significant clinical problem. Also the author describes fundic gland polyps (but not gastric adenomas) and then in brackets discusses gastric cancer and risk. This is very confusing. Firstly because although there is some debate, it is most likely that fundic gland polyps are not -pre-malignant.
Secondly whether or not there is an increased of gastric cancer in FAP is debatable and the literature describes an increased risk in SE Asia but no increased risk in the Western world.

4. "Peri-ampullary carcinoma" is not a specific feature of Gardner's syndrome, rather duodenal and ampullary adenoma and carcinoma are an important manifestation FAP in general, with or without the other extra-colonic manifestations described.

5. As before, attenuated FAP needs a clearer description - most would insert an age at which the polyp count is <100.

FAP SUBTYPES

1. I think that this section could be better used to get rid of some old fashioned/unhelpful terms and also to clarify the genetic diversity causing adenomatous polyposis syndromes. This is better than calling it FAP subtypes.

2. CNS tumors are recognised extra-colonic manifestations of both FAP and Lynch syndrome. Turcot's syndrome is unhelpful as it does not distinguish these genetic distinct diseases also FAP CNS tumours are usually medulloblastomas and often appear in childhood. CNS tumours in Lynch are usually later presenting and are mostly glioblastomas. Neither FAP nor Lynch syndrome are inherited in a recessive manner. If there are reports of recessive inheritance, this should be referenced and the paradox explained further.

3. Hereditary desmoid disease, is fully explained by the genotype-phenotype correlation in FAP. It would be helpful to make this clearer, as hereditary desmoid disease really is "just" FAP with the manifestations one would expect given the 3' mutations identified.

4. The description of MAP, NAP and PPAP shows why labelling them as subtypes of FAP is really unhelpful and misleading. MAP and NAP and been assigned FAP2 and 3 respectively, yet PPAP does not carry a subgrouping. In addition the text makes it clear that the clinical manifestations of these syndromes can be remarkably different to FAP eg desmoids only seen in FAP; NAP and PPAP (possibly MAP) have cancer risks not associated with FAP. Finally the genetic causes are distinct and the inheritance patterns may differ to FAP; trying to put them all together under the umbrella term FAP is therefore unhelpful.

GENOTYPE-PHENOTYPE CORRELATIONS AND MIDOFIER ALLELES

1. It would be helpful to have a figure showing the genotype-phenotype correlation in FAP ie those with a germline APC mutation
2. Desmoid risk is not just associated with codons 1310 and 2011. In addition family history represents a risk for desmoid, independent of germline mutation, which may represent the action of a modifier gene - please see Sturt N et al GUT 2004

3. A summary table highlighting FAP, MAP, NAP, PPAP genetics, inheritance and clinical manifestations would be helpful.

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