Reviewer’s report

Title: A rare missense variant in APC interrupts splicing and causes AFAP in two Danish families

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Reviewer: Annemieke van der Hout

Reviewer's report:

This is a clearly written report, which is of interest for everyone who is involved in (molecularly) diagnosing FAP. It is good to have an emphasis on a cryptic splice site mutation, a group of mutations which is in the highly automated genome diagnostics of today easily overlooked. I have two comments:

1. The classification of c.289G>A, p.(Gly97Arg) as a pathogenic mutation and the cause of APC in these families would even be stronger if it was possible to show that from the mutant allele only the (-70) transcript is produced. Is there a SNP close enough to the mutation to distinguish the mutant and the WT allele in a Sanger sequencing experiment?

2. The same mutation c.289G>A, p.(Gly97Arg) in APC was recently described in a Chinese pedigree with mild FAP (Wang (2019) Med Sci Monit 25, 3796). This information should be added to the manuscript, as it is a strong argument against c.289G>A, p.(Gly97Arg) being a rare Danish SNP unrelated to FAP.

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