Bridging the gap in GAPPS: Clinical testing, characteristic features, and gastric cancer screening

Kory Jasperson[1], Andrea Hawrysh[2], Marcy Richardson[1], Emily Stephenson[2], Tina Pesaran[1], Brandon Smith[1], AJ Stuenkel[1]

[1]Ambry Genetics, Aliso Viejo, California, USA

[2]Kingston General Hospital, Kingston, Ontario, Canada

Background: Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) is a newly-described syndrome characterized by diffuse fundic gland polyps (FGPs) and an increased risk of gastric cancer. Point mutations in the YY1 binding motif of *APC* promoter 1B were recently found to cause GAPPS. Here we describe the results of clinical testing for GAPPS in individuals primarily suspicious for familial adenomatous polyposis (FAP) and/or attenuated FAP.

Methods: Data from clinical testing of *APC*-only and *APC* plus *MUTYH* from 01/06/2017-03/31/2017 at Ambry Genetics were retrospectively reviewed. Comprehensive *APC* testing was performed, including sequencing of the YY1 motif. *APC* alterations classified as pathogenic or likely pathogenic were included.

Results: There were 28 *APC*-only and 58 *APC* plus *MUTYH* tests, with nine and five *APC* mutations found, respectively (Table 1). Only one YY1 point mutation (c.-191 T>C) was found in the *APC*-only cohort and accounted for 11.1% of all mutations detected in that group. The clinical histories are described for the YY1 positive case and two of her positive relatives (Figure1).

Conclusions: Promoter 1B YY1 sequencing is now available and should be included in *APC* clinical testing. Dysplasia in FGPs is common in GAPPS and should be an indication for *APC* genetic testing, regardless of other history. A positive family history may not be present in cases with GAPPS, as FGPs may be underreported in families. Gastric cancer screening in the proband was unsuccessful, as over 20 gastroscopies revealed no cancer, including one two months prior to her stage IV diagnosis.