INTRODUCTION

Lynch syndrome is an autosomal dominant genetic syndrome that, in the United States, is thought to be responsible for up to 4% of colorectal cancer diagnoses. It is also known to contribute to the prevalence of additional cancers, most notably endometrial, ovarian and gastric. Laboratories continue to add genes to Lynch syndrome clinical analyses as they are discovered and validated. As of 2011, testing at Myriad included both sequencing and large rearrangement analysis of MLH1, MSH2, MSH6, PMS2, and EPCAM.

The analysis of additional genes leads to an initial rise in the rate of detection of variants of uncertain significance (VUS). VUSs have an unknown effect on protein production/function and present a challenge to the clinician in how to determine the most appropriate patient medical management. Clinical laboratories can utilize various strategies to help clarify the significance of VUS in order to provide clinicians with more definitive risk information.

This poster presents the current deleterious mutation distribution, mutation type (sequencing vs. large rearrangement), and the VUS rate.

METHODS

To determine the mutation distribution, clinical test results were analyzed for patients who were referred for clinical genetic testing of the Lynch syndrome associated genes. In order to assess variant rates in Lynch syndrome testing over time, we reviewed MLH1/MSH2/MSH6 variant rates from 2006 to 2013 as well as PMS2 rates from 2011 to 2013.

RESULTS

Since 2006, over 53,000 patients have had testing for Lynch syndrome through Myriad. Seven percent of those patients have had a positive test result (deleterious or suspected deleterious mutation). Figure 1 shows the distribution of deleterious mutations found in patients by gene. Figure 3 and Figure 4 show the distribution of the two major types of deleterious mutations, i.e. sequence vs. large rearrangements.

In addition to deleterious mutations, VUSs have also been identified in Lynch syndrome genes. The current VUS rate for MLH1/MSH2/MSH6/EPCAM is 5.8% and 2.6% for PMS2. The decline in VUS rate is dependent on dedicated resources and on the validated variant reclassification techniques employed by the testing laboratory. The reclassification techniques used in our laboratory are shown in Figure 5. Figure 6 illustrates the declining VUS rate over time with Figure 2 depicting the current VUS rates for each Lynch syndrome gene.

DISCUSSION

While novel variants are still discovered in Lynch syndrome genes on a regular basis, there has been a steady decline in the percentages of VUSs reported by our laboratory. Myriad uses multiple methods for accurate reclassification which has resulted in rapid decreases in the number of variant results. New methods for reclassification are being continually assessed.

CONCLUSIONS

Lynch syndrome testing has improved through the stepwise addition of genes, allowing for increased sensitivity, and validated reclassification methodologies, that have decreased the VUS rate, allowing for more definitive interpretation of results.

REFERENCES


Conflict of Interest: All authors are employees of Myriad Genetic Laboratories, Inc., and receive salary and stock as compensation.