Clinical Diagnostic PMS2 Testing in a Single Commercial Laboratory: Challenges in Gross Deletion/Duplication Analysis Due to PMS2CL Interference

Selvi Palaniappan 1, Carin Espenschied1, Jenna Guilltian1, Amal Yussuf1, David Salvador1, Chia-Ling Gau1, Brian Shirts2

1Ambyr Genetics Aliso Viejo, CA, 2Department of Laboratory Medicine, University of Washington Seattle, WA

BACKGROUND

- Lynch syndrome is the most common cause of hereditary colorectal cancer and is due to mutations in MLH1, MSH2/EPICAM, MSH6 or PMS2
- Recent data suggests that PMS2 may account for up to 24% of Lynch syndrome cases1.
- PMS2 testing is complicated by the presence of pseudogenes. PMS2CL, one of the pseudogenes, has close homology to PMS2 exons 11 to 15 2.
- When alterations are found in this region via NGS and/or MLPA, additional methodologies are necessary to determine if the alteration is in PMS2 or PMS2CL3
- While these Sanger sequencing protocols can correctly identify the location for single nucleotide variants and small indels, available methodologies are sometimes unable to identify the location of gross deletions/duplications (del/dup) found in exons 11 to 15.
- To better understand the impact of PMS2CL interference, we analyzed PMS2 results in a large cohort of patients undergoing testing for PMS2 either via multi-gene panel testing (MGPT) or Lynch syndrome testing.

METHODS

- Results of PMS2 clinical testing via MGPT (N=82,667) or Lynch syndrome testing (N=5,488) from June 2010 through June 2016 at a single laboratory were analyzed.
- Gross del/dup in exons 11 -15 were analyzed in detail to determine the effect of PMS2CL interference.

RESULTS

- Overall positive rate for PMS2 was 0.07% and VUS rate was 1.88%.
- Lynch syndrome test positive rate: 5.47% 
- MGPT positive rate: 0.43%
- 153 (0.17%) patients had a del/dup in PMS2 exons 1-11.
- 334 (0.38%) patients had a del/dup in exons 11-15 requiring follow-up analysis. Using available methodologies, they were assigned as follows: PMS2 (N= 99, 0.12%) MGPT (N=168, 0.19%)
- Inconclusive (N=67, 0.07%); due to close homology.
- The most common del/dups in PMS2 were Ex11dup (N=19, 19.19%), Ex14_15del (N=15, 15.15%) and Ex14del (N=20, 20.20%), and Ex11dup (partial) (N=12, 12.12%)
- The most common PMS2CL del/dup was Ex13CL_14CLdel (N=129, 76.78%)
- Of these 69.76% were of African/African American descent (90/129).
- 74.62% of the inconclusive results (50/67) were Ex13_14del.

TAKE-HOME POINTS

- The majority (68.58%) of PMS2 gross del/dups occur between exons 11-15 and available methodologies are able to determine the location in a most of these cases: PMS2 (29.28%) or in PMS2CL (50.00%).
- Comprehensive analysis using additional methodologies is necessary when a sequence alteration and/or large del/dup are found between exons 11-15.
- Ex13CL_14CLdel is the most common deletion in PMS2CL (76.78%) and may be common in the African population.
- Ex13_14del is also accounts for the majority of difficult to assign cases, due to close homology of PMS2 and PMS2CL and limitations in current methodologies.
- Further studies and development of alternative methodologies are needed to determine the location of a large deletion/duplication located between exons 11-15.

REFERENCES