Abstract Preview

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- Do not use all caps
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RNA-seq Identifies Structural Variants in Hereditary Cancer Genes

B. Conner[1], M. Richardson[2], F. Hernandez[2], T. Landrith[1], T. McBride[2], B. Tippin-Davis[1], R. Karam[1]. 1) Research & Development, Ambry Genetics, Aliso Viejo, CA; 2) Clinical Diagnostics, Ambry Genetics, Aliso Viejo, CA.

Introduction: Massively parallel RNA sequencing (RNA-seq) is able to identify structural variants (SV) in *MSH2,* a frequent site for this type of alteration due to its enrichment with intronic Alu elements[1,2]. We have expanded upon this previously reported *MSH2* cohort to investigate, by RNA-seq, other SV in additional Lynch Syndrome (LS) and hereditary breast and ovarian cancer (HBOC) genes.

Methods: RNA-seq was performed as described previously in the whole blood of patients identified with germline SV[1]. Reads supporting aberrant splicing of the involved exons were used as one line of evidence for variant classification using ACMG/AMP guidelines[3]. All study participants consented to RNA genetic testing on a research basis.

Results: A set of 15 SV were reclassified from variant of unknown significance (VUS) to clinically actionable pathogenic/likely pathogenic variants (LP) or likely benign (LB). RNA genetic testing provided evidence for reclassification of SV in the following HBOC genes: *BARD1* (n=1), *BRCA1* (n=3), *BRIP1* (n=1), *CHEK2* (n=2), *PTEN* (n=1), *PALB2* (n=1), *RAD50* (n=1). Nine exonic duplications had reads supporting aberrant splicing and were determined to be in-tandem, resulting in their reclassification from VUS to LP. *RAD50* EX8dup was found to have a mid exonic breakpoint and there was no evidence of aberrant splicing by RNA-seq. This evidence was used to reclassify the variant from VUS to LB.

The previously reported *MSH2* duplication cohort was expanded upon by adding *MSH2* EX3_6dup. SV in the following LS genes were also analyzed: *MLH1* (n=3), *PMS2* (n=1). RNA genetic testing identified aberrant splicing in all five LS SV, leading to their reclassification from VUS to LP.

Discussion: RNA-seq has clinical utility as RNA evidence carries strong weight in the ACMG/AMP variant classification guidelines[3]. This proves to be a high-throughput approach by which variants can be reclassified from VUS to either benign or pathogenic/likely pathogenic. Such reclassifications empower clinicians to offer the appropriate clinical management to LS and HBOC patients.

References:

1. Conner et al 2019
2. Mu et al 2019
3. Richards et al 2015

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