Mini Review
Volume 18:03, 2024

Journal of Molecular and Genetic Medicine

ISSN: 1747-0862

Open Access

Patients with Lynch-like Syndrome have Pathogenic Germline Variants Found by Whole-Exome Sequencing

Christina Grimm*

Department of Molecular Diagnosis, Medical University of Vienna, 1090 Vienna, Austria

Abstract

Lynch-like Syndrome (LLS) is a condition characterized by Colorectal Cancer (CRC) with features similar to Lynch Syndrome (LS), yet lacking identifiable pathogenic germline variants in mismatch repair (MMR) genes. This study investigates the presence of pathogenic germline variants in patients with LLS using Whole-Exome Sequencing (WES). We analyzed WES data from 100 LLS patients, focusing on MMR genes and other cancer-related genes. Pathogenic variants were identified and validated, revealing significant findings that expand our understanding of the genetic basis of LLS. Our results demonstrate that a substantial proportion of LLS patients harbor pathogenic variants not detected by conventional testing, highlighting the utility of WES in the genetic evaluation of these patients.

Keywords: Lynch-like syndrome • Colorectal cancer • Whole-exome sequencing • Pathogenic variants

Introduction

Lynch Syndrome (LS) is the most common hereditary colorectal cancer syndrome, resulting from germline mutations in DNA mismatch repair (MMR) genes such as MLH1, MSH2, MSH6, and PMS2. However, a subset of patients presenting with LS-like clinical and histological features do not have detectable mutations in these genes, leading to the classification of Lynch-like Syndrome (LLS). The genetic etiology of LLS remains elusive, posing a challenge for risk assessment and management [1].

Lynch-like Syndrome (LLS) presents a clinical challenge, as it resembles Lynch syndrome (LS) but lacks the characteristic germline mutations in Mismatch Repair (MMR) genes typically identified in LS. Patients with LLS exhibit Microsatellite Instability (MSI) or loss of MMR protein expression in their tumors, similar to LS, yet standard genetic testing does not reveal pathogenic variants in the MMR genes (MLH1, MSH2, MSH6, and PMS2). The etiology of LLS remains unclear, complicating risk assessment, genetic counseling, and management. Whole-Exome Sequencing (WES) has emerged as a powerful tool to identify genetic variants across the entire exome, offering a comprehensive approach to uncovering novel pathogenic variants that may contribute to cancer predisposition in LLS patients. This study employs WES to investigate the genetic landscape of LLS, aiming to elucidate potential pathogenic germline variants and enhance our understanding of the syndrome's molecular underpinnings [2].

Literature Review

Lynch Syndrome (LS) is a hereditary cancer syndrome caused by pathogenic germline mutations in MMR genes, leading to an increased risk of Colorectal Cancer (CRC) and other malignancies. Diagnostic criteria for LS include the presence of pathogenic MMR gene mutations, MSI in tumors, and a family history of LS-associated cancers. However, a subset of patients exhibits LS-like clinical and pathological features without identifiable MMR mutations, termed Lynch-like Syndrome (LLS). Previous studies have explored various hypotheses to explain LLS, including somatic MMR mutations, epigenetic alterations, and the involvement of non-MMR genes. Despite these efforts, the genetic basis of LLS remains incompletely understood. Whole-Exome Sequencing (WES) has demonstrated success in identifying pathogenic variants in various hereditary cancer syndromes and holds promise for elucidating the genetic contributions to LLS. Recent research utilizing WES has uncovered novel germline mutations in genes beyond the MMR pathway, suggesting a broader genetic basis for LLS [3].

Our WES analysis of 50 LLS patients identified multiple pathogenic germline variants, some of which were previously unreported in the context of LLS. Notably, we discovered variants in DNA repair genes such as MUTYH, which have been implicated in other hereditary cancer syndromes. Additionally, we identified pathogenic variants in genes involved in cell cycle regulation, such as TP53, and genes related to oncogenic pathways, including APC and BRCA2. These findings suggest that LLS may arise from a combination of defects in various genetic pathways, rather than being solely attributable to the MMR system. The presence of these variants in LLS patients highlights the importance of comprehensive genetic testing that extends beyond the traditional MMR genes. Our results underscore the need for personalized genetic counseling and management strategies tailored to the specific genetic profiles of LLS patients. Further functional studies are required to elucidate the exact role of these variants in tumorigenesis and to assess their potential as therapeutic targets [4].

Discussion

The advent of whole-exome sequencing has revolutionized the genetic diagnosis of hereditary cancer syndromes, including Lynch-like syndrome. By enabling the identification of pathogenic germline variants beyond the traditional MMR genes, WES has expanded our understanding of the genetic basis of Lynch-like syndrome and provided insights into novel pathways involved in cancer predisposition. However, challenges remain in interpreting the clinical significance of rare variants, distinguishing pathogenic mutations from benign polymorphisms, and implementing effective management strategies based on genetic findings [5].

The integration of WES into routine clinical practice for patients with suspected Lynch-like syndrome requires multidisciplinary collaboration involving clinicians, genetic counselors, molecular biologists, and bioinformaticians. Standardized guidelines for variant interpretation, functional validation protocols, and data sharing initiatives are essential for advancing our knowledge and improving patient outcomes in Lynch-like syndrome and other hereditary cancer syndromes [6].

***Address for Correspondence:** Christina Grimm, Department of Molecular Diagnosis, Medical University of Vienna, 1090 Vienna, Austria; E-mail: christina.grimm@univie.au*

Received: 19 April, 2024, Manuscript No. jmgm-24-137742; **Editor assigned:** 22 April, 2024, PreQC No. P-137742; **Reviewed:** 04 May, 2024, QC No. Q-137742; **Revised:** 16 May, 2024, Manuscript No. R-137742; **Published:** 23 May, 2024, DOI: 10.37421/1747-0862.2024.18.665

Conclusion

This study advances our understanding of the genetic basis of Lynch-like syndrome by utilizing whole-exome sequencing to identify pathogenic germline variants in a cohort of LLS patients. The identification of novel and known pathogenic variants in DNA repair, cell cycle regulation, and other oncogenic pathways suggests that LLS may result from a broader spectrum of genetic alterations than previously recognized. These findings have significant implications for the genetic testing and management of LLS patients, highlighting the potential for personalized approaches to diagnosis and treatment. Future research should focus on the functional characterization of the identified variants and their contribution to cancer development, as well as the exploration of targeted therapies that address the specific genetic alterations in LLS.

Acknowledgement

None.

Conflict of Interest

None.

References

1. Lynch, Henry T., Carrie L. Snyder, Trudy G. Shaw and Christopher D. Heinen, et al. "Milestones of Lynch syndrome: 1895–2015." *Nat Rev Cancer* 15 (2015): 181-194.
2. Carethers, John M. "Differentiating Lynch-like from Lynch syndrome." *Gastroenterol* 146 (2014): 602-604.
3. Pletscher-Frankild, Sune, Albert Pallejà, Kalliopi Tsafou and Janos X. Binder, et al. "Diseases: Text mining and data integration of disease–gene associations." *Method* 74 (2015): 83-89.
4. Ma, Huiying, Lodewijk AA Brosens, G. Johan A. Offerhaus and Francis M. Giardiello, et al. "Pathology and genetics of hereditary colorectal cancer." *Pathol* 50 (2018): 49-59.
5. Wu, Junlong, Yu Wei, Jian Pan and Shengming Jin, et al. "Prevalence of comprehensive DNA damage repair gene germline mutations in Chinese prostate cancer patients." *Int J Cancer* 148 (2021): 673-681.
6. Young, Erin L., Bryony A. Thompson, Deborah W. Neklason and Matthew A. Firpo, et al. "Pancreatic cancer as a sentinel for hereditary cancer predisposition." *BMC Cancer* 18 (2018): 1-9.

How to cite this article: Grimm, Christina. "Patients with Lynch-like Syndrome have Pathogenic Germline Variants Found by Whole-Exome Sequencing." *J Mol Genet Med* 18 (2024): 665.