Genetics in Medicine (2022) 24, S26–43

ELSEVIER

Genetics in Medicine

www.journals.elsevier.com/genetics-in-medicine

Cancer Genetics and Therapeutics Abstracts (poster)

eP039

Does Lynch syndrome cause predisposition to breast cancer? Experience from a hereditary breast cancer clinic in Pakistan

Fizza Akbar[1], Zahraa Siddiqui[1], M. Talha Waheed[1], Lubaina Ehsan[2], Khurram Minhas[1], Abida Sattar[1], Salman Kirmani[1]

[1]The Aga Khan University; [2]School of Medicine, Western Michigan University Stryker, MI

Background: Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer syndrome, is an autosomal dominant disorder caused by the presence of germline pathogenic (P) or likely pathogenic (LP) variants in DNA mismatch repair (MMR) genes, which include *MLH1, MSH2, MSH6, PMS2,* and *EPCAM*. Presence of a disease-causing variant in any of these MMR genes increases an individual's lifetime risk of developing colorectal cancer (CRC) (61%), endometrial (57%), ovarian (38%), renal pelvis or ureter (28%), prostate (24%), breast (19%), small bowel (11%), gastric (9%), brain (8%), hepatobiliary cancer (4%) and pancreatic cancer (2%). It is still unclear whether LS causes a predisposition to breast cancer, with current data suggesting a risk < 15%, which is close to the general population risk of 13%. Guidelines for high-risk surveillance and management of individuals with LS are thus not well-established for breast cancer, which at present is to be managed based on family history.

Identification of germline disease-causing variants in MMR genes is thus pivotal for optimizing the treatment and surveillance of patients with LS and for the identification of at-risk family members, to reduce cancer-related morbidity and mortality. This is best done using Next Generation Sequencing (NGS) multi-gene panel testing, which increases the diagnostic yield, but also increases the chances of finding variants of uncertain significance (VUS). As the Pakistani population remains under-represented, the likelihood of finding a VUS is high, making it difficult to use these results for clinical decision-making.

Objectives: • To study the presence of disease-causing variants as well as VUSs in MMR genes causing LS in a series of patients diagnosed with breast cancer who underwent genetic testing using a multi-gene NGS panel

• To study the clinical characteristics of patients with LS who presented with breast cancer

• To use immunohistochemistry (IHC) on breast tumour tissue samples to clarify whether VUSs in MMR genes in breast cancer patients are associated with loss of staining.

Methods: Retrospective chart review of patients who visited the hereditary cancer (HBC) clinic and proceeded with Hereditary Breast and Gynecological Cancer multi-gene NGS panel testing (at Prevention Genetic and Invitae Genetics, USA) from May 2017 to Oct 2021, at an Academic Medical Centre, Aga Khan University Hospital, Karachi, Pakistan. IHC was performed using standard antibodies against the protein products of *MLH1, MSH2, MSH6* and *PMS2*.

Results and Discussion: A total of 460 breast cancer patients qualified and proceeded with testing, considering their personal and/or family history of disease, based on NCCN criteria. 94 patients (20.4%) had a positive genetic test result, which included Pathogenic (P) and Likely Pathogenic (LP) variants. Of the remaining patients, 167 (36.3%) had one or more VUS[s], and 199 (43.3%) had a negative genetic test result.

Five out the total 460 patients (1.1%) or five of the 94 patients with positive results (5.3%), tested positive for LS, with an average age at diagnosis of 40 years. One patient had a personal history of colon cancer at age 38 and had then presented with breast cancer at age 43; and had a family history of colon cancer. Another patient who presented with breast cancer only, harbored a pathogenic variant in *MSH6* as well as *BRCA1,* having a positive family history of breast and uterine cancer. In the remaining three patients, personal or family history was not indicative of any possible established link with LS, and their diagnoses would have been missed if MMR genes were not included in the multi-gene panel. Thus, multi-gene testing including MMR genes increased the diagnostic yield by 4.3% (4/94), even after excluding the patient with a personal history of colon cancer. Details of these patients are mentioned in Table 1.

Out of the total 460 patients who underwent testing, 28 (6.1%) harbored a VUS in MMR genes, namely *PMS2* (n=12), *MSH2* (n=7), *MSH6* (n=8) and one patient had a VUS in both PMS2 and *MSH2*. No VUS in *MLH1* was identified in breast cancer patients.

IHC was done on 18/28 (64.3%) and no loss of staining was observed on any tissue sample, possibly indicating that the variants are not disease-causing. We also observed six recurrent VUSs in unrelated patients, which included, (variant.1) v.1: *MSH2* NM_000251.2 (p.L135V) (Rs193096019 MAF in South Asians=0.05%), v.2: *MSH6* NM_000179.2 (p.L1356Dfs*4), (rs775836476, MAF in South Asians=0.04%), v.3: *MSH6, (p.R911Q),* (Rs761622304,MAF in South Asians= 0.006%), *v.4: PMS2* NM_000535.5 (p.R294W) (rs563433235, MAF in South Asians= 0.03%), *v.5: PMS2 (*p.L454S) (absent from population database), *v.6: PMS2* (p.D784N) (unreliable region coverage).It is worth noting that, v. 2, 4 and 6 have been reported in diseased individuals, while v.5 is a novel variant, absent from the gnomAD, highlighting the need for further functional studies to understanding the role of these variants in tumorigenesis.

Conclusions: In our experience with genetic testing in the HBC, a small proportion of patients were diagnosed with Lynch Syndrome, some presenting with breast cancer alone, without a personal or family history of LS associated tumors. This may justify the need to include MMR genes in multi-gene panels being offered to breast cancer patients. VUSs in these genes remain challenging, especially in underrepresented populations, and IHC may be a way to at least partially clarify their significance. More ethno-specific genomic studies, as well as better functional studies are required provide better clinical care.

Patient ID	Variant detail	Age at diagnosis	Tumor IHC	Histopathology	Secondary cancer, age	Family History
1	*MLH1, NM_000249.3, Deletion (Exons 16-19)*	43	ER+/PR+, HER2-	IDC Grade II	Ca Colon	father, ca colon
2	*MSH6, NM_000179.2, c.3261del (p. F1088Sfs*2)* *BRCA1, NM_007294.3, Deletion (Exons 1-2)*	30	Triple Negative Disease	IDC Grade III	-	mother, maternal aunts, grandmother, ca breast and uterine
3	*MLH1*, NM_000249.3, Exon 3, c.306G>T (p. E102D)	39	ER+/PR+, HER2-	IDC Grade II	-	sister, ca breast
4	*MLH1*, NM_000249.3, Intron 16, c.1897-2A>G	60	Triple Negative Disease	IDC (Grade not available)	-	sister, cousins, ca breast
5	*MSH6*, NM_000179.2, Exon 4 c.1222_1226del (p.P408Dfs*8),	30	ER-/PR-, HER2+	DCIS	-	Negative

IHC= Immunohistochemistry, IDC= Invasive Ductal Carcinoma, DCIS= In-situ Ductal Carcinoma, ER= estrogen receptor, PR=progesterone receptor HER2= Human Epidermal Growth Factor Receptor 2

https://doi.org/10.1016/j.gim.2022.01.077

eP040

Breast cancer patients categorized as high-risk of recurrence and/or basal-type molecular subtype by Agendia should universally undergo germline genetic testing

Brenna Bentley[1], Chloe Wernecke[1], Kelly Bontempo[1], Maureen Graham[1], Pat Whitworth[2], Rakesh Patel[1], Peter Beitsch[1]

[1]*Medneon;* [2]*TME*

Introduction: With the rise of somatic testing, more physicians are using panels to understand the genetic profile of breast cancer to help aid in clinical management. Agendia, a molecular diagnostics company focused on breast cancer, has developed two tests to support clinical decisions. MammaPrint analyzes 70 genes associated with breast cancer recurrence and reports whether an individual has a low (1.3%) or high (11.7%) risk for recurrence. BluePrint analyzes 80 genes to identify the breast cancer's molecular subtype: Luminal A (low-risk), Luminal B (high-risk), HER2 (respond well to HER2-targeted therapies), and Basal-Type (aggressive subtype). However, little is known about the relationship between the results of Agendia's tests and the likelihood of identifying an underlying germline variant. We hypothesize that individuals in the High-Risk category on MammaPrint, and individuals with Basal subtype are more likely to have positive germline genetic results indicating the presence of a pathogenic or likely pathogenic variant.
Methods: Patient data was obtained from the Informed Genetics Annotated Patient Registry (iGAP), an IRB-approved multi-centered longitudinal, observational study designed to capture genetic and genomic test results and their utilization and impact on treatment practices and outcomes to help determine the most effective use of testing in real-world patient populations and to support access to advances in precision medicine. Of the 2,439 subjects currently enrolled in the registry, 1,231 have been diagnosed with breast cancer (50.47%). 267 individuals underwent tumor profiling through Agendia's MammaPrint and/or BluePrint as well as germline genetic testing. Descriptive statistics were used to assess and compare data of these populations.
Results: Results indicate that of the 267 individuals who were tested through Agendia's MammaPrint (239) and/or BluePrint (127) panels and underwent germline genetic testing, 135 (56.49%) were classified as High-Risk for recurrence on MammaPrint, and 104 (45.51%) were identified as having a Low-Risk for recurrence. Individuals with a high-risk of recurrence had a 10.04% positive germline variant rate compared to the low-risk group with a 5.44% positive rate. 127 individuals with breast cancer were tested and categorized through Agendia's BluePrint panel. Eight were classified as Basal type, 2 as HER2 type, 58 as Luminal A type, 35 as Luminal B type, and 24 a Luminal type unspecified. Individuals with Luminal A type had the highest positive germline rate of 45.67%, compared to HER2 (1.57%), Basal (6.30%), Luminal B (27.56%), and Luminal unspecified (18.90%).
Conclusion: The iGAP real-world evidence database revealed that individuals categorized as having a high risk of breast cancer recurrence through Agendia's MammaPrint were identified to harbor a pathogenic or likely pathogenic variant 10.04% of the time. An even higher likelihood (45.67%, 27.56%, and 18.90%) was seen in individuals with a Luminal A, Luminal B, and Luminal unspecified molecular subtype, respectively. This data argues that germline genetic testing should be offered to every individual, regardless of age, identified as having a high risk of breast cancer recurrence and/or a Luminal-type molecular subtype on Agendia's tests. Identification of a pathogenic or likely pathogenic variant has clinical management, familial, and potentially reproductive implications.

https://doi.org/10.1016/j.gim.2022.01.078

eP041

How long will they wait? Applying updated NCCN criteria to previously unqualified patients reveals missed opportunities for personalized cancer management

Kelly Bontempo[1], Eric Brown[2], Chloe Wernecke[1], Brenna Bentley[1], Krista Ortega[1], Jessica Kreamer[3], Peter Beitsch[2], Rakesh Patel[2]

[1]*Medneon;* [2]*Targeted Medical Education;* [3]*Northwestern University*

Introduction: Uncovering germline genetic variants responsible for cancer predisposition allows providers to implement personalized medical care for patients. The NCCN Guidelines were designed to help identify individuals who qualify for genetic testing, yet multiple studies have shown that approximately half of patients with pathogenic or likely pathogenic variants are missed using these guidelines. While guidelines have continued to evolve as more robust data have