

Patterns and Frequency of Pathogenic Germline Variants Among Prostate Cancer Patients Utilizing Multi-Gene Panel Genetic Testing

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Abstract

Background: Germline genetic testing (GGT) has significant implications in the management of patients with prostate cancer (PCa). Herein, we report on patterns and frequency of pathogenic/likely pathogenic germline variants (P/LPGVs) among newly diagnosed Arab patients with PCa.

Methods: Patients meeting the National Comprehensive Cancer Network (NCCN) eligibility criteria for GGT were offered a 19-gene PCa panel or an expanded 84-gene multi-cancer panel.

Results: During the study period, 231 patients were enrolled; 107 (46.3%) had metastatic disease at diagnosis. In total, 17 P/LPGVs were detected in 17 patients (7.4%). Among the 113 (48.9%) patients who underwent GGT with the 19-gene panel, eight (7.1%) had P/LPGVs, compared to nine (7.6%) of the 118 (51.1%) who did GGT through the expanded 84-gene panel ($P = 0.88$). Variant of uncertain significance (VUS) rate was higher ($n = 73$, 61.9%) among the group who underwent expanded 84-gene panel testing compared to those who underwent the 19-gene PCa panel ($n = 35$, 30.9%) ($P = 0.001$). P/LPGVs in DNA damage repair (DDR) genes, most frequently *BRCA2*, *CHEK2* and *TP53*, were the most common P/LPGVs findings.

Conclusion: This study is the first to characterize the germline genetic profile of an Arab population with PCa. All detected P/LPGVs were potentially actionable, with most variants able to be detected with a PCa-specific panel.

Keywords: Prostate cancer; Germline testing; Pathogenic mutations; VUS; *BRCA*

Introduction

Prostate cancer (PCa) is the second most common cancer diagnosed among men worldwide and its incidence is highest in Western societies [1]. Treatment options for localized disease include active surveillance, radical prostatectomy, or radiotherapy. Selection of the treatment modality is typically dependent on a multi-disciplinary approach that incorporates risk category, performance status, associated comorbidities, and patients' preference [1, 2]. The standard of care for patients with metastatic disease has shifted towards early therapy intensification, which involves combining androgen deprivation therapy (ADT) with either docetaxel or a novel oral androgen signaling inhibitor. This approach has demonstrated improved outcomes compared to ADT alone [2-5].

Despite the progress made in treating localized and metastatic PCa, a considerable number of patients still experience poor outcomes. Expanding our knowledge of molecular biomarkers and pathogenic/likely pathogenic germline variants (P/LPGVs) holds promise in revealing valuable insights into the diverse characteristics and outcomes of these patients, and in informing treatment decisions. New studies are shedding light on multiple genomic and environmental risk factors in PCa. Nevertheless, current understanding of the influence of these factors on outcomes is still limited [6].

Over the last decade, there has been a heightened interest in the inherited component of PCa, as these P/LPGVs may have implications on screening and treatment decisions [7-9]. Germline genetic testing (GGT) identifies a spectrum of cancer predisposition variants, from low to high risk. At least 170 inherited variants have been identified, which are involved in about one-third of familial PCa cases. This list includes DNA damage repair (DDR) genes such as *ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *MLH1*, *MSH2*, *MSH6*, *NBN*, *PALB2* and *PMS2* [8-10], some of which are predictive of unfavorable prognosis irrespective of disease stage and may guide treatment selec-

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tion, such as the use of poly-ADP ribose polymerase (PARP) inhibitors in patients with metastatic PCa who harbor germline *BRCA1/2* mutations [8-12]. Accordingly, current guidelines, including the National Comprehensive Cancer Network (NCCN), the Philadelphia expert consensus (2019) and the American Urological Association (AUA), endorse GGT for PCa with minor differences between these guidelines regarding the panel of genes to be tested and the eligibility criteria [13-15]. Currently, NCCN guidelines recommend GGT for patients with high-risk localized, locally advanced and metastatic disease, or for patients with positive family history for cancer such as prostate and hereditary breast and ovarian syndromes, regardless of the disease stage [13].

The distribution of many P/LPGVs varies according to ethnicity and geographic region; however, data on the P/LPGV landscape of PCa patients from the Middle East region remain scarce. Herein, we prospectively investigated patients who were treated at King Hussein Cancer Center, aiming to identify the patterns and frequency of P/LPGVs in this population. Moreover, we sought to explore the additional value of expanded multi-gene panel testing (MGPT) for detection of additional P/LPGVs not captured with more limited MGPT.

Materials and Methods

Patient population

This was a prospective, single-institution study of P/LPGVs among newly diagnosed patients with prostatic adenocarcinoma treated at King Hussein Cancer Center from March 2021 to July 2022. Eligibility criteria included: age ≥ 18 years of Arab descent who met the NCCN criteria (version 1.2020) for GGT. Eligible men were stratified according to castrate status as per NCCN definition; castration resistance is defined as any biochemical, radiographic, or clinical progression, with serum testosterone < 50 ng/mL after hormonal therapy [16].

Genetic counseling

Patients were approached through the genetic counseling clinic, and those who met the NCCN criteria were offered GGT with either a 19-gene PCa panel ("prostate MGPT") or an expanded 84-gene multi-cancer panel ("multi-cancer MGPT"), per patient choice. The prostate MGPT consists of 10 genes with established evidence for PCa and recommended by NCCN (*ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *HOXB13*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, and *PMS2*), in addition to nine other genes with preliminary evidence for PCa risk (*EPCAM*, *NBN*, *TP53*, *ATR*, *BRIP1*, *FANCA*, *GEN1*, *RAD51C* and *RAD51D*). The multi-cancer MGPT consists of 84 genes associated with various hereditary cancer syndromes (Supplementary Material 1, www.wjon.org). Full-gene sequencing, deletion/duplication analysis, and variant interpretation were performed at a single commercial laboratory (Invitae Corporation, San Francisco, CA, USA), as previously described [17, 18]. Results were reported according to the American College of Medical Ge-

netics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) five tiers classification: pathogenic (P), likely pathogenic (LP), variant of uncertain significance (VUS), likely benign and benign. Variants were classified as positive (≥ 1 P/LP), VUS (≥ 1 VUS in the absence of a P/LPGV) and negative (no P/LP or VUS identified). Carriers of single P/LPGV in genes associated with autosomal recessive inheritance (e.g., *MUTYH*) were not counted in the overall P/LPGV yield. NCCN guidelines recommend GGT for patients with high-risk localized and metastatic disease, or for patients with positive family history for cancer such as prostate and hereditary breast and ovarian syndromes, regardless of the disease stage [13]. Results were sent to the treating physician and the genetic counselor disclosed results to the patient.

Genetic testing

Patients' identifiers were coded, and all GGT was performed on DNA extracted using a peripheral blood sample at a reference laboratory (Invitae Corporation) for both the limited and the expanded 84-gene MGP. Whole gene sequencing was performed utilizing a next-generation sequencing (NGS) platform as previously described [17, 18].

Data collection and study procedures

Electronic medical records were accessed to obtain demographics and clinical data. Cancer family history was obtained during the genetic counseling consultation. Demographics, clinical characteristics, cancer family history and GGT results were documented in a Health Insurance Portability and Accountability Act (HIPAA)-compliant database. Research was performed in accordance with relevant local and international guidelines and regulations including the Declaration of Helsinki. The study was approved by the King Hussein Cancer Center Institutional Review Board (IRB) and registered under Clinicaltrial.gov identifier: NCT04920513.

Statistical analysis

Descriptive statistics were utilized to report means, median, standard deviations, and proportions. The Chi-square test was used to compare the rate of detection of P/LPGV and VUS and to explore the correlation between disease characteristics and the likelihood of identifying a P/LPGV; all P-values less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 19 (SPSS Inc., Chicago, IL).

Results

Patient characteristics

A total of 266 patients were identified as eligible for GGT. After providing genetic counseling, 35 (13.1%) patients de-

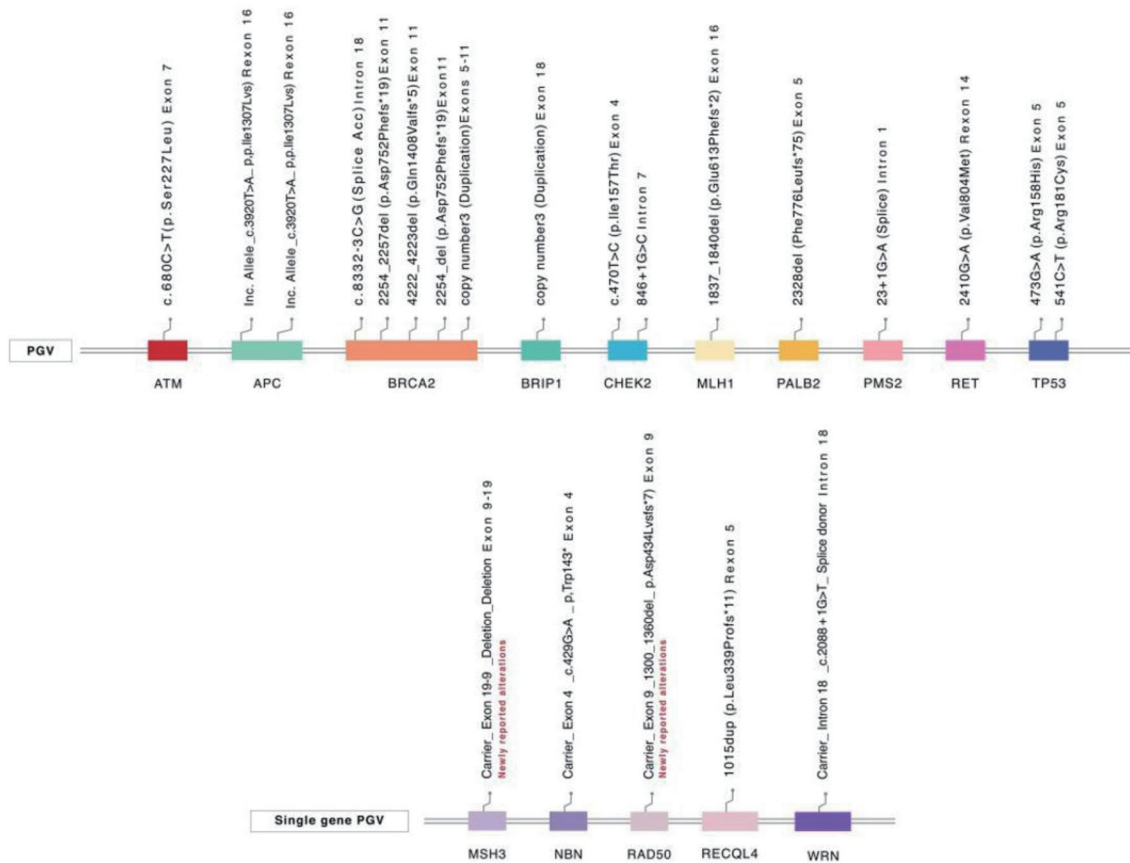


Figure 1. Pathogenic/likely pathogenic variants. PGV: pathogenic germline variant.

clined GGT; the majority (n = 24; 68.6%) did not believe in the value of GGT while seven (20.0%) were concerned about the stress related to results and an additional four (11.4%) declined testing for financial reasons. The remaining 231 patients underwent GGT and comprised the cohort for analysis. The median age at diagnosis was 67 (range, 45 - 86) years, 124 (53.7%) patients had localized disease while 107 (46.3%) had metastatic disease. The median baseline serum prostate-specific antigen (PSA) value was 32 (range, 2.4 - 3,975) ng/mL, and 146 (63.2%) of patients had a Gleason score \geq 8. The most frequent indication for GGT was localized high-risk disease in 115 (49.8%) or metastatic in 107 (46.3%) and nine (3.9%) with positive family history for cancer. A total of 113 (48.9%) patients elected to do prostate MGPT, while the other 118 (51.1%) patients opted for multi-cancer MGPT. Both groups were balanced in terms of their clinical characteristics.

Genetic testing results

A total of 17 P/LPGV were identified in 17 (7.4%) patients. Among the 113 patients who underwent prostate MGPT, eight (7.1%) had P/LPGV, compared to nine (7.6%) among the 118 who had multi-cancer MGPT (P = 0.88). P/LPGVs were as follows: 14 patients (82.4%) had P/LPGV in DDR genes including ATM (n = 1), BRCA2 (n = 5), BRIP1 (n = 1), CHEK2 (n = 2),

MLH1 (n = 1), PALB2 (n=1), PMS2 (n = 1), and TP53 (n = 2). Additional P/LPGV findings included RET (n = 1) and APC I1307K (n = 2) (Fig. 1). Notably, an additional five patients, not included in the total P/LPGV yield above, were identified as carriers of a single P/LPGV in a gene associated with an autosomal recessive cancer syndrome (one patient each with MSH3, NBN, RAD50, RECQL4, and WRN). Of these alterations, WRN (Intron 18; c.2088+1G>T (splice donor)) and MSH3 (deletion exon 9-19) have not been previously documented in ClinVar (Supplementary Material 2, www.wjon.org).

Only three of the detected P/LPGVs were not included in the PCa MGPT (RET and APC). Notably, there were no significant differences in P/LPGV frequency by various clinical characteristics, including castration status (sensitive vs. resistant), age (\leq 65 vs. $>$ 65), Gleason score (\geq 8 vs. $<$ 8), disease stage (localized vs. metastatic) or family history (Table 1). All detected P/LPGVs were actionable based on published management guidelines (n = 17) or potential eligibility for clinical trials and/or targeted therapies (n = 12).

VUS

The most frequently observed alterations in the whole cohort were VUS in 108 (46.8%) patients with the absence of a P/LPGV. VUSs were more commonly detected with the multi-

Table 1. PGV Rates Across Clinical Variables (n = 231)

Characteristics	N (%)	PGVs, N (%)	P-value
Age at diagnosis (years)			0.542
Median (range)	67 (45 - 86)		
≤ 65	106 (48.9)	9 (8.5)	
≥ 65	125 (54.1)	8 (6.4)	
Genetic testing			0.884
Prostate MGPT	113 (48.9)	8 (7.1)	
Multi-cancer MGPT	118 (51.1)	9 (7.6)	
Gleason score			0.935
< 8	77 (33.3)	6 (7.8)	
≥ 8	146 (63.2)	11 (7.5)	
Stage at diagnosis			0.582
Localized	124 (53.7)	8 (6.5)	
Metastatic	107 (46.3)	9 (8.4)	
Castration status			0.794
Sensitive	65 (28.1)	5 (7.7)	
Resistant	44 (19.0)	4 (9.1)	
Family history			0.414
Positive	171 (74.0)	14 (8.2)	
Negative	60 (26.0)	3 (5.0)	

MGPT: multi-gene panel testing; PGVs: pathogenic germline variants.

cancer MGPT (n = 73, 61.9%), compared to the PCa MGPT (n = 35, 30.9%) (P < 0.001).

Discussion

To the best of our knowledge, this is the first study to examine the prevalence and characteristics of P/LPGV in Arab PCa patients. The first comprehensive GGT study in PCa was published by Pritchard et al in 2016. Their study examined 692 patients with metastatic disease, who were unselected by family history or age at diagnosis. The study reported an 11.8% prevalence of P/LPGV in DNA repair genes. Notably, this frequency was significantly higher than that observed in a cohort of 499 patients with localized disease, where only 4.9% had P/LPGV in DNA repair genes [19]. Subsequent studies, including both retrospective and prospective unselected cohorts, have reported P/LPGV prevalence ranging from 8% to 20% [20, 21].

The prevalence of P/LPGV in our patient population is slightly lower (7.4%) than has been reported in the aforementioned studies [22-24]; however, it is similar to the yield recently reported by Shore et al (7.7%) in a prospective GGT study of unselected PCa where the majority had low-grade localized disease [25]. Similar to our study, their P/LPGV yield excluded carriers of single P/LPGV in autosomal recessive cancer syndrome genes. Various factors contribute to the range of P/LPGV identified, including study design whether retrospective or prospective, patient characteristics, including the proportion of metastatic or advanced disease, in addition

to specific criteria used for GGT eligibility, and differences in testing methodologies or genes included on MGPT. Furthermore, racial disparities in P/LPGV rates may contribute to this variation. A recent study by Giri et al highlighted the discrepancy in P/LPGV rates between PCa patients of different ethnicities in the USA. The frequency of P/LPGV was notably higher in White patients (11%) compared to Black/African American patients (5.9%) [21]. This is not unexpected given the over-representation of White European participants in the genetic studies that inform GGT criteria and variant interpretation databases, resulting in higher rates of uncertain findings and lower rates of definitive molecular diagnoses in individuals from historically underrepresented non-White populations, including Arab patients [26-28]. This is evident in a study from Korea which reported P/LPGV in 5.8% of tested Korean men with mutations similar to our study [29]. Furthermore, many studies have documented higher P/LPGV prevalence in metastatic castrate-resistant PCa (mCRPC) compared with castrate-sensitive cases, nevertheless, our results did not show a significant difference between the two groups, though this may be due to our study being under-powered to detect the difference between these two groups.

Consistent with other data from literature [20, 21, 30], our study showed that the most prevalent P/LPGVs in PCa were in homologous recombination repair (HRR) genes, whereas only 0.9% had DNA mismatch repair (MMR) gene alterations. Notably, we reported two cases (12% of positive results) of the increased risk allele *APC I1307K*, which is associated with increased risk for colorectal cancer and is prevalent among Ash-

kenazi Jews [24]; the high incidence in the Arab population warrants further investigation. We acknowledge that it is controversial to classify mutations such as *APC* *I1307K* CHEK2 c.470T>C as pathogenic, given their high prevalence in general population. This is another hot area for future research.

The NCCN PCa GGT guidelines (version 4.2023) recommend testing of 10 genes; however, most commercial laboratories offer customized panels with specific add-on genes with preliminary evidence. The prostate MGPT we utilized for testing included nine additional non-NCCN genes, which resulted in the identification of three additional P/LPGVs. Multi-cancer MPGT resulted in the detection of only three additional P/LPGVs (two *APC* and one *RET* with *RECQL4* as a carrier finding). Multi-cancer MGPT was associated with a statistically significant increase in VUS. However, patients with VUS should be managed based on their personal and family history as the majority of VUSs are ultimately reclassified to benign [31-33]. Nevertheless, detecting these VUSs in understudied population, such as our population, might result in reclassification of some of these genes to P/LPGV. Meanwhile, VUS can significantly increase anxiety and psychological distress for both patients and physicians, because of the uncertainty of VUS impacts. However, knowledge accumulation would be useful in future genetic research, moreover patients and families with VUS can be notified when the gene is reclassified.

Notably, four patients were found to have alteration in a gene associated with autosomal recessive cancer inheritance. While these findings may not directly impact cancer risk, they can be important for cascade testing, and in the case of DDR genes such as *NBN* and *RAD50*, may even qualify patients for clinical trials (NCT03413995, NCT03209401). Interestingly, the *WRN* (splice site) and *MSH3* (deletion) variants detected in our study have not been reported in the literature or public databases. Furthermore, the other two identified P/LPGVs (*RAD50* and *NBN*) have been reported in breast cancer but not in PCa [22, 23]. Additional studies are warranted to assess the significance of these alterations in PCa. Another observation in our study was the *TP53* mutation in the context of Li-Fraumeni spectrum cancers, as the two patients with *TP53* had family history for malignancy. One had family history of lung, breast, colorectal, lymphoma and kidney cancers in first-degree relatives. While the second had family history of breast cancer and PCa in three of his relatives.

GGT plays a crucial role in precision medicine, by providing relevant prognostic information and identifying gene alterations that could serve as therapeutic targets. Accumulating data confirm the clinical activity of PARP inhibitors in patients with germline and somatic DDR gene alterations [8, 34, 35]. In the PROfound trial, olaparib showed improved radiographic progression-free survival (rPFS) and overall survival (OS) in mCRPC compared to novel hormonal agents, particularly in patients with *BRCA1/2* or *ATM* alterations, and these findings led to FDA approval in May 2020 [36, 37]. Another trial, TRITON 3, evaluated rucaparib in mCRPC patients with deleterious alterations in *BRCA1*, *BRCA2*, or *ATM*, showing improved rPFS compared to investigator's choice treatment in patients with *BRCA1/BRCA2* alterations but not in those with *ATM* alterations [35]. Recently, the FDA approved the combination of olaparib and abiraterone with prednisolone in patients with

BRCA-mutated mCRPC based on data from the PROPEL trial, demonstrating improved rPFS and OS compared to abiraterone and prednisolone. This improvement was observed in patients with *BRCA* mutations but not in those without *BRCA* mutations [38]. More recently, niraparib has been approved in combination with abiraterone in first line setting for somatic *BRCA*-mutated mCRPC based on the phase 3 MAGNITUDE study [39-41]. Noteworthy, these trials have mainly included somatic rather than germline mutations.

The prevalence of *MMR* P/LPGV in advanced PCa has been reported to be 0.5-1.7% [8, 42-45]. Thus, our 0.9% rate of *MMR* genes is consistent with the literature. However, the two patients with *MMR* aberrations in our cohort had alterations in *MLH1* and *PMS2* genes, in contrast to the *MSH2* and *MSH6* P/LPGV most commonly reported in other PCa studies [42-44]. Current evidence shows a two to threefold higher frequency of *MMR* mutations in metastatic PCa compared to localized disease [45]. Aside from the advanced disease stage, there is a higher likelihood of identifying *MMR* P/LPGV in patients with Gleason score ≥ 8 and ductal histologic variants [46, 47]. Up to 12% of patients with metastatic PCa are found to have somatic *MMR* gene mutations and/or microsatellite instability (MSI)-high status [45]. Identification of a P/LPGV in an *MMR* gene is often an indication that the tumor may be *MMR*-deficient, and the patient may therefore be eligible for treatment with the FDA-approved immune checkpoint inhibitor pembrolizumab [48, 49].

In our study, we found that all identified P/LPGVs, most of which were in the DDR pathway, were actionable based on published management guidelines, or potential eligibility for clinical trials and/or targeted therapies. This suggests that patients carrying these genes may potentially benefit from novel drugs. These variants may also play a crucial role in determining disease prognosis and personalized management plans. Moreover, the detection of these P/LPGVs enables cancer screening and prevention of the patients and their families.

We conducted prospective GGT of 231 men. However, it is worth noting that the majority of men with PCa in our region are not offered GGT, even when they meet the recommendations set by major professional societies. This disparity can be attributed to many factors such as a lack of genetic counselors, insufficient knowledge among treating physicians, and a lack of insurance coverage. It is important to acknowledge that these barriers are not limited to our region alone. A survey conducted by the Prostate Cancer Clinical Trial Consortium revealed that less than 40% of treating physicians in academic centers refer eligible candidates for GGT, and only 12% of individuals with high-risk localized disease were considered for testing [50]. In our study, we encountered a refusal rate of 13% among patients, and interestingly, the main reasons for this were disbelief in the value of GGT, and concern about the social and psychological impact of receiving positive results. These findings warrant further investigation and targeted interventions.

Finally, we acknowledge some limitations relevant to our study. First, our study did not include disease and treatment outcomes, which could have provided valuable insights into the correlation between GGT and patients' prognosis. Second, although our cohort included a significant number of patients

relative to disease prevalence in our region, it is still a small cohort compared to other studies in the literature. Third, we failed to identify a significant correlation between many patient and disease characteristics and the likelihood of increased detection of P/LPGV, which could require a larger sample size. Nevertheless, this study contributes valuable information to the literature regarding the germline genetic profile of Arab patients with PCa.

Conclusions

Our study represents the first report of GGT conducted in an Arab population with PCa. Among patients tested, 7.4% exhibited P/LPGV, mostly involving DDR genes. We observed that a panel of 19 prostate-specific genes was effective in identifying the majority of P/LPGV. More studies are needed to correlate these GGT results with clinical outcomes in our PCa patient population.

Supplementary Material

Suppl 1. List of tested genes.

Suppl 2. Details of pathogenic/likely pathogenic/increased risk allele germline mutations.

Acknowledgments

None to declare.

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Conflict of Interest

Edward D. Esplin and Sarah M. Nielsen are employees and shareholders of Invitae Corp. Brandie Heald are former employees and shareholders of Invitae Corp. Edward D. Esplin is an advisor and stockholder of Taproot Health and Exir Bio. All listed authors have no conflict of interest to declare.

Informed Consent

All enrolled patients signed consent forms.

Author Contributions

Conceptualization: HAR. Data curation: RAH, SS, RG, AA, HBH. Formal analysis: HAR, HBH, RAH, SS. Investigation:

SMN, BS, HBH. Project administration: HAR, SMN, HBH. Supervision: HAR, HBH, RAH. Writing-original draft: RAH, HAR. Writing-review and editing: HAR, RAH, BS, SMN, BH, EDS, HBH, SS, RG, AA, TA, YA.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request. All variants were submitted to ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar/>).

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