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Case report

ADAMTS14, *ARHGAP22*, and *EPDR1* as potential novel targets in acute myeloid leukaemia

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ABSTRACT

Acute myeloid leukaemia (AML) is a blood cancer with a heterogeneous genomic landscape. This study aimed to mine bioinformatics data generated by RNA sequencing to unveil an AML case transcriptome profile and identify novel therapeutic targets and markers. In this study, we have determined the transcriptomic profile and analysed gene variants of an AML patient at the time of diagnosis and validated some genes by quantitative reverse transcriptase polymerase chain reaction. *ADAMTS14*, *ARHGAP22*, and *ependymin-related protein 1* (*EPDR1*) were markedly upregulated compared to the corresponding control. In addition, novel exonic single-nucleotide and insertion/deletion variants were identified in these genes. Hence, *ADAMTS14*, *ARHGAP22*, and *EPDR1* can be proposed as potential novel targets in AML, and their exact roles should be further explored.

1. Introduction

Acute myeloid leukaemia (AML) is a heterogeneous blood cancer with a poor prognosis and complex classification owing to its complicated genetic landscape. This may reflect sophisticated gene expression machinery, which consolidates AML cells; therefore, disease targeting is more challenging [1, 2]. Genetic alterations that cause AML have been postulated to affect cellular processes related to survival, proliferation, differentiation, apoptosis, and epigenetic changes [3, 4]. A study [5] conducted large-scale genomic sequencing to understand the complex landscape of AML. They classified genetic alterations in their study sample into four major classes—changes in coding regions, splice variants, genomic regulatory regions, and non-repetitive sequences. Among the genetic events, several known AML-initiating genetic fusions, such as *MLL*, *PML-RARA*, and *RUNX1-RUNX1T1* fusions, were reported in the study. In addition, mutations in *FLT3*, *NPM1*, and other genes were identified in the study. Moreover, less frequent mutations in AML, such as those in *SMC1A* and *AMC3*, were also observed [5]. Similarly, whole transcriptomic analysis revealed a large number of fusion events in AML and myelodysplastic syndrome; these novel fusions were observed in a single patient with AML, and these genetic events were associated with p53 mutations and a sophisticated karyotype profile [6]. Hence, it is clear that AML has a complex molecular basis, which contributes to poor disease prognosis and difficult therapeutic targeting. Therefore, this study aimed to introduce potential novel targets/gene variants identified by RNA sequencing in AML that could serve as promising therapeutic targets in this type of blood cancer.

2. Case presentation

A 37-year-old woman was incidentally found to have pancytopaenia. She was well until approximately 2 weeks prior to presentation to our hospital with bone pain and general weakness. Clinical examination did not reveal lymphadenopathy or organomegaly. A complete blood count test showed a white blood cell count of 8.6×10^3/μL, haemoglobin level of 10 g/dl, and platelet count of 62×10^3/μL, which decreased to 45×10^3/μL when rechecked the next day. A peripheral blood smear showed blast counts of 40%, 30%, and 41% on three checks performed on two successive days. The patient was diagnosed with acute myeloid leukaemia. The cytogenetic report of bone marrow aspiration indicated the presence of an abnormal tumour clone with trisomy 8 (47, XX, +8[18]/46, XX[1]), which was confirmed by fluorescence in situ hybridisation (FISH), and showed 88% trisomy 8. The patient was treated with induction chemotherapy consisting of Daunorubicin and Cytarabine. The patient has achieved remission, and was then treated by allogeneic bone marrow transplantation. However, the patient died 7 months after diagnosis.

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3. Methods

The study was reviewed and approved by the Institutional Review Board (IRB) of Imam Abdurrahman Bin Faisal University and King Fahd Teaching Hospital of the University (IRB# 2017-03-147), and patient consent was obtained prior to participation. Once the initial diagnosis was suggested by the haematopathologist, a blood sample was collected into a 'PAXgene Blood RNA tube (Preanalytix, Hombrechtikon, Switzerland)', and then RNA was extracted and sequenced [7, 8] to elucidate the whole-transcriptome profile of the disease at the time of diagnosis before treatment. RNA was extracted according to the protocol described in the PAXgene Blood RNA Kit (#762164; Preanalytix, Hombrechtikon Switzerland). RNA concentration, integrity, and 28s/18s ribosomal RNA ratio were analysed using an Agilent 2100 bioanalyzer with an Agilent RNA 6000 nano kit (5067-1511, Agilent Technologies, Germany). A cDNA library was constructed for sequencing using the BGISEQ-500 platform, starting from mRNA enrichment to depletion of rRNA in the sample. This was followed by fragmentation, cDNA synthesis, adaptor ligation, poly A tailing at 3′ end, polymerase chain reaction (PCR) amplification, denaturation, cyclisation, and sequencing on the BGISEQ-500 platform.

Gene expression was quantified using the RNA-Seq by Expectation Maximization (RSEM) package [9], and the NOIseq method [10] was used to derive data plots. The quantity of gene transcripts was measured as

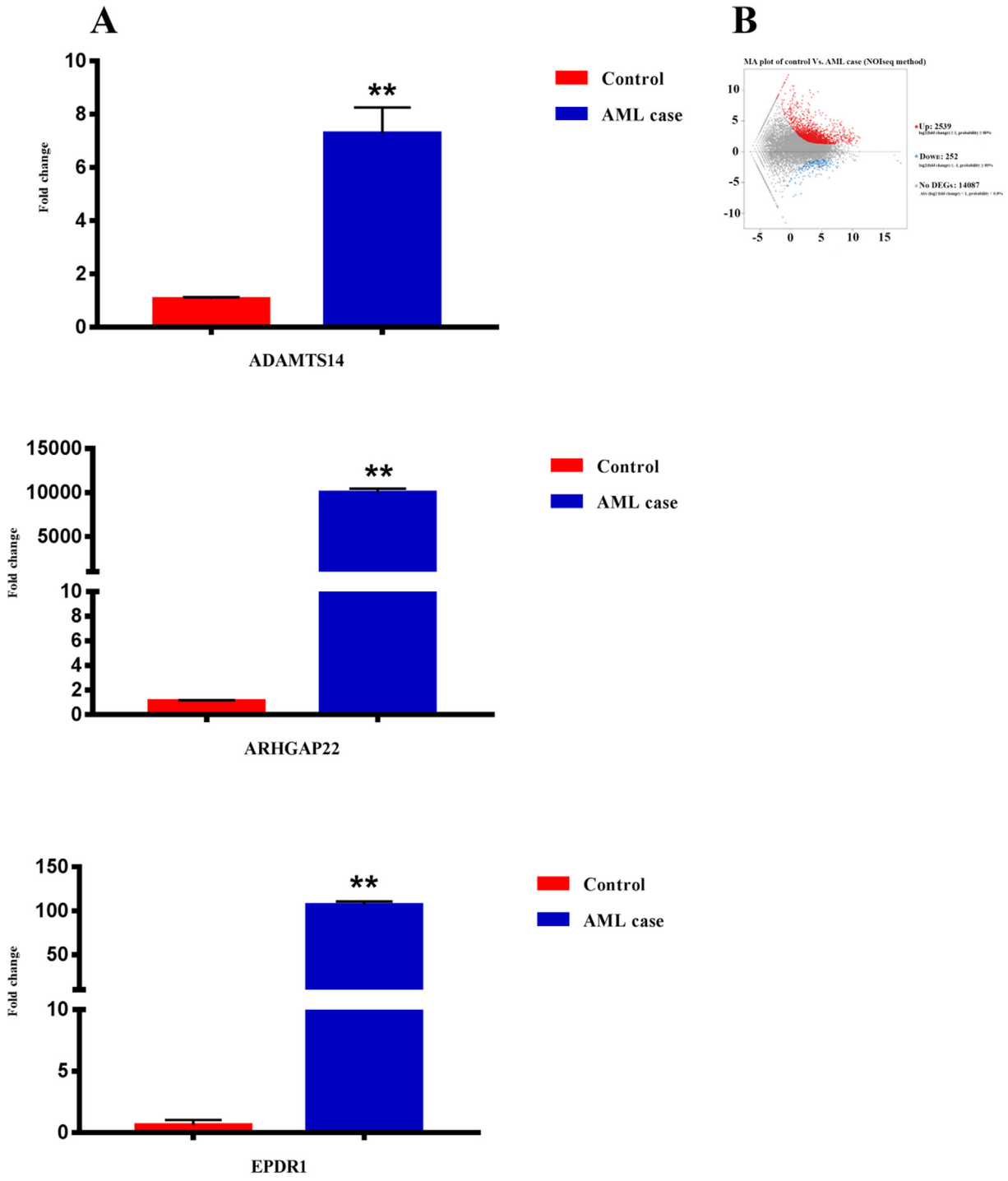

Figure 1. Relative gene expression of *ADAMTS14*, *ARHGAP22* and *EPDR1* and MA plot of differentially expressed genes in a newly diagnosed AML case.

Table 1. RNA sequencing and qPCR fold change values for *ADAMTS14*, *ARHGAP22*, and *EPDR1*.

Gene name	Log_2 fold change	Actual fold change	Probability of gene expression	qPCR fold change
ADAMTS14	6.02	64.9	89.7%	7.28
ARHGAP22	6.02	64.9	97.3%	10005.6
EPDR1	7.33	160.9	97.07%	106.37

Table 2. Summary of novel transcript variants reported for the patient with AML.

Transcripts	Number
Novel transcripts	10,444
Novel splicing variants of known genes	8,033
Novel genes	1,251

fragments per kilobase of transcript per million mapped reads. NOIseq algorithms [10, 11] were then used to screen the differentially expressed genes and calculate the probabilities of differential gene expression by calculating the log_2 ratio of expression between the test and control and the difference between the two conditions. The probability of gene expression was then obtained by comparing these values to the noise distribution; if the odds of probability of differential expression/non-differential expression were more than a certain threshold, the gene was considered differentially expressed between the test and the control. This indicates that the detected gene transcripts are not technique-related artefacts, which was verified by q-RT-PCR results (Figure 1). Genes with $\geq$1 log_2 fold change and $\geq$80% probability were considered upregulated, while those with $\leq$-1 log_2 fold change and $\geq$80% probability were considered downregulated compared to the corresponding control. The transcriptomic profile was compared to a healthy age-matched female control profile. Genes were filtered, and some genes with a probability of gene expression of $\geq$80% and $\geq$5 log_2 fold change were further validated by quantitative (q) reverse transcriptase (RT) PCR. The validated genes were *ADAMTS14* (forward primer: ATGACCCCTTTGATCCTGCC; reverse primer: GGTCTGGTAGCCACTGCCAA), *ARHGAP22* (forward primer: TTCTGCGGCCACAGGTAGAG; reverse primer: CCGTGAAGAGCTGGCTGTGT), and ependymin-related protein 1 (*EPDR1*; forward primer: CGCGGTTTTTTGACATCCAG; reverse primer: CCAGGAGCAGTCTTCGCTCA). In brief, samples were tested in triplicate using Qiagen qPCR master mix in the ABI 7 PCR instrument. The cycling program was 2 min at 95 °C, followed by 40 cycles (10 s at 95 °C, 10 s at 59 °C, and 40 s at 72 °C). The final reaction volume was 16 μL, containing 1 μL of the reverse-transcribed cDNA template. β-actin was used as an internal control gene, and the cycling threshold (Ct) was determined using a corrected threshold value. Relative gene expression was quantified using the $2^{-\Delta\Delta Ct}$ method. Single nucleotide polymorphism (SNP) and insertion/-deletion (INDEL) analyses were performed to identify gene variants.

4. Results

RNA sequencing results revealed upregulation of a significant number of genes compared to the corresponding control profile; the number of upregulated genes was remarkable compared to the number of downregulated genes (2539 vs. 252, Figure 1). *ADAMTS14*, *ARHGAP22*, and *EPDR1* were among the top 8% upregulated genes and q-RT-PCR results reflected their transcripts overexpression revealed by RNA sequencing. The fold change values and probabilities of gene expression for these genes, indicated by RNA sequencing and real-time qPCR, are summarised in Figure 1 and Table 1, which illustrate the number of times the three genes were overexpressed in the present patient with AML compared to their expression level in the corresponding control. By investigating the publicly available TCGA database of mRNA expression of 200 AML patients at cBioPortal [12], it was found that the gene expression of *ADAMTS14* was not significantly different between the living group and the deceased group ($p = 0.921$). The same nonsignificant difference was cited for the expression of *ARHGAP22* and *EPDR1* ($p = 0.939$ and 0.0592, respectively) suggesting that they are not associated with disease outcomes in this cohort.

q-RT-PCR fold-change values (A) revealing a remarkable relative gene expression of *ADAMTS14*, *ARHGAP22*, and *EPDR1* in the AML case compared to that in the corresponding control. The MA plot (B) revealing the differentially expressed genes in the AML case, indicating a large number of upregulated genes compared to the control. The difference between gene expression in the AML case patient and control was statistically significant. Experiments were performed as duplicate samples, each in triplicate sets and data were presented as means with standard deviation. ** = p value $\leq$0.01 as concluded by unpaired t-test.

SNP and mutation analyses revealed a significant number of genetic variations [13]; the number of novel transcripts is summarised in Table 2. Among them, exonic *NRAS* mutations, intronic mutations in nucleophosmin (*NPM1*), and intronic and exonic mutations in fms-like tyrosine kinase 3 (*FLT3*) have been detected [13]. It was previously reported that specific mutations in *NPM1*, *NRAS* and *FLT3* are common genetic signatures in AML [14, 15, 16]. It is noteworthy to indicate that the clinical significance of the gene variants of *NPM1*, *NRAS* and *FLT3* that we are reporting of this case patient in association with AML is not reported.

Table 3. INDEL analysis of *ADAMTS14, ARHGAP22,* and *EPDR1* in the case patient with AML.

Gene name	Reference sequence	AML case sequence	Location	Insertion/ deletion	Position	Chromosome
ADAMTS14	ATAGT	A	Intron	Deletion	72508479 (R)	10
	CA	C	Intron	Deletion	72513344 (N)	
	TAG	T	Intron	Deletion	72514575 (N)	
	CA	C	Intron	Deletion	72515069 (R)	
	CGCT	C	Intron	Deletion	72519859 (R)	
	GA	G	Exon	Deletion	72521913 (N)	
	C	CAAAAAA	Exon	Insertion	72522193 (N)	
ARHGAP22	CG	C	Down 2K	Deletion	49653853 (R)	10
	TTGC	T	Intron	Deletion	49660899 (N)	
	G	GAATA	Intron	Insertion	49668786 (N)	
	GC	G	Intron	Deletion	49674312 (R)	
	C	CT	Intron	Insertion	49675498 (N)	
	CT	C	Intron	Deletion	49703681 (N)	
EPDR1	TG	T	Intron	Deletion	37985249 (N)	7

N = novel and R = reported (gene variants were verified using the Database of Single Nucleotide Polymorphisms) [16].

Table 4. Exonic SNPS of *ADAMTS14*, *ARHGAP22*, and *EPDR1* in the patient with AML.

Gene name	Reference sequence	AML case sequence	Number of exonic SNPS/total number of SNPS	SNP position	Chromosome
ADAMTS14	T	G	17/55	72432306 (R)	10
	C	A		72432498 (R)	
	A	C		72432521 (R)	
	G	T		72468504 (N)	
	T	C		72500763 (R)	
	C	T		72513682 (R)	
	C	T		72517837 (R)	
	A	G		72520330 (R)	
	A	G		72520567 (R)	
	C	T		72520726 (R)	
	G	A		72521155 (R)	
	T	C		72521175 (R)	
	C	G		72521309 (R)	
	T	C		72521422 (R)	
	C	T		72521651 (R)	
	C	T		72522088 (R)	
	A	G		72522189 (R)	
ARHGAP22	A	G	6/70	49654195 (R)	10
	C	T		49654342 (R)	
	C	T		49654403 (R)	
	T	C		49667795 (R)	
	G	A		49687800 (R)	
	C	A		49701645 (N)	
EPDR1	No exonic SNPs were detected				7

N = novel and R = reported (gene variants were verified using the Database of Single Nucleotide Polymorphisms) [16].

Also, a known synonymous variant in CCAAT enhancer binding protein alpha (*CEBPA*) was found in the present AML case patient. The SNV genomic position is 19: 33792631; C > A and this variant is associated with benign clinical significance in AML [17, 18]. Likewise, two known synonymous variants were also found in *RUNX1* in the present AML case patient (genome positions 21: 36164789; C > G and 36171638; G > A). Both variants have benign clinical association with myeloid malignancy [19, 20]. Additionally, two novel insertion variants were also found in core-binding factor subunit beta (*CBFB*) (genomic positions 16: 67133068; A > AT and 16: 67133322; C > CT) with unknown clinical significance. Gene variants of *CBFB*, *CEBPA*, *NPM1*, *NRAS*, *FLT3*, and *RUNX1* that were found in the AML case patient were reported in the supplementary file (Tables S1-S9). In order to compare our results with a publicly available database that was concluded from a larger study sample, we explored the TCGA, PanCancer Atlas database of acute myeloid leukemia that was published at "cBioPortal for cancer genomics" [21]. The data indicated that the frequency of mutations in these known AML genomic signatures were 29.5% for *FLT3*, 27% (*NPM1*), 8% (*NRAS*), 9.5% (*RUNX1*), 6.5% (*CEBPA*), and *CBFB* was found to be mutated in 1% of the 200 patients. In addition, INDEL and SNP analyses of *ADAMTS14*, *ARHGAP22*, and *EPDR1* are presented in Tables 3 and 4 (for simplicity, only exonic SNPs have been presented). The results of INDEL and SNP analyses were verified using the Database of Single Nucleotide Polymorphisms [22]. Likewise, searching the TCGA, PanCancer Atlas database [21] for the candidate genes revealed that *ADAMTS14* was not reported amongst the mutated genes; however, other *ADAMTS* isoforms were found to be mutated in these patients' samples, including *ADAMTS* 1, 6, 9, 12, and 16–19. Similarly, other *ARHGAP* isoforms were mutated in these patients (*ARHGAP* 5, 6, 18, 21, 24–26, 31, 32, 35, 36, 39, 40, and 44). A deletion alteration in *ARHGAP 22* was also reported in only 0.5% of patients (10q11.22-q). *EPDR1* mutations were not reported in this database.

To this end, the overall survival analysis showed that 33.5% of all patients whose data were included in this statistical analysis (186 cases) had events-free survival. The overall survival of the deceased cases (95% confidence interval) was 8.98 months (7.04–11.01). Referring to the gene variants, there was no significant difference between the two groups regarding the number of nonsynonymous mutations ($p = 0.198$) and the tumor mutational burden (TMB) ($p = 0.198$). Specifically, there was no significant difference in the frequency of *FLT3* alteration between the living and the deceased groups (29.85 vs. 30.83; $p = 0.511$). The difference in the frequency of *NPM1* and *RUNX1* alterations between the two groups was also not significant ($p = 0.298$ and 0.412, respectively) [21, 23].

5. Discussion and conclusion

AML is considered the most heterogeneous type of blood cancer and is associated with a poor prognosis. Disease risk stratification is essential for proper and successful clinical management. Whole-genome sequencing approaches have greatly helped with respect to this [24]. However, disease complexity signifies the need for the continuous exploration of disease profiles in different patient groups to identify potential therapeutic targets. Thus, we used whole-transcriptome sequencing to determine the landscape of gene expression at the time of diagnosis in a patient with AML. A remarkable gene expression profile was observed, particularly a high number of upregulated genes.

ADAMTS14 is a member of a large protein family known as a disintegrin-like metalloproteinase domain with thrombospondin motifs. Polymorphism in *ADAMTS14* has been reported in patients with oral cancer and is associated with tumour promotion and degree of differentiation [25]. In the present study, four novel INDEL variants and one novel exonic SNP were identified in *ADAMTS14* (Tables 3 and 4). In line with this, another study linked *ADAMTS14* polymorphisms to

progression of hepatocellular carcinoma [26]. In contrast, lower expression of *ADAMTS14* was proposed as a factor that could contribute to a poor prognosis and worse overall survival rates in patients with oral squamous cell carcinoma [27]. In the current study, bioinformatics data revealed remarkable overexpression of *ADAMTS14* in the blood cells of the case patient with AML, a finding that was validated by qPCR. This suggests that *ADAMTS14* can be a potential novel target in AML, whose role should be thoroughly investigated in the disease.

In addition, Rho GTPase activating protein 22 (*ARHGAP22* [RhoGAP2 or RhoGAP22]), which is overexpressed in the present case patient with AML, is another candidate on the list. The gene belongs to a large family of proteins in which *ARHGAP27* has been characterised and its implication in chronic lymphocytic leukaemia has been postulated [28]. In addition, *ARHGAP22* is implicated in tumour cell motility [29]. For example, its mediation of melanoma cell movement has been documented [30]. In addition, *ARHGAP22* is phosphorylated downstream of Akt signalling, suggesting its involvement in the survival-mediated influence of this famous kinase [31]. Notably, novel INDEL and SNP variants in *ARHGAP22* were also identified (Tables 3 and 4).

The third proposed candidate, *EPDR1*, was originally identified as a batokine with a potentially important role in metabolic regulation. Recently, overexpression of this protein was found to be positively correlated with colorectal cancer proliferation and invasiveness in a cohort study [32]. Similarly, high levels of *EPDR1* are correlated with the advancement of hepatocellular carcinoma stages, making it a potential biomarker for disease progression and monitoring [33]. Further, *EPDR1* is associated with KRAS mutations, confirmed by in silico RNA sequencing results, a mechanism that has been implicated in colorectal cancer resistance [34]. Consistent with these results, *EPDR1* was overexpressed in the case patient with AML in this study, as confirmed by RNA sequencing and qPCR. Recently, *EPDR1* has been found to be one of the most upregulated genes downstream of the NO66 protein in an AML cell line model. NO66 has been found to be a possible regulator of myeloid stem and progenitor cells proliferation and maturation [35]. This supports our hypothesis that the upregulation of *EPDR1* in patients with AML should be further assessed. Taken together, the remarkable upregulation of the three genes and their association with AML should be confirmed in a larger study. Likewise, one novel deletion variant of *EPDR1* was identified in our patient with AML.

To the best of our knowledge, *ADAMTS14*, *ARHGAP22*, and *EPDR1* have not been previously reported in AML, except for *EPDR1*, which has been recently reported. To this end, we introduced *ADAMTS14*, *ARHGAP22*, and *EPDR1* as potential novel targets in acute myeloid leukaemia. However, we recommend that the findings of the present study should be confirmed in a larger cohort of patients with AML. In this context, TCGA database provided bioinformatics analysis of 200 samples [12] and showed that the expression of the 3 candidate genes was not significantly associated with overall survival of patients. This suggests that they are not probably involved in disease prognosis. However, the present study showed the remarkable overexpression of the 3 genes in comparison to healthy control at the time of diagnosis, which urges further investigation of their implications in disease initiation and perhaps potential use as biomarkers.

6. Institutional review board statement

This study was reviewed and approved by the Institutional Review Board (IRB) of Imam Abdulrahman Bin Faisal University (IRB# 2017-03-147).

7. Informed consent statement

Informed consent was obtained from all participants prior to their enrolment in the study.

Declarations

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

Supplementary content related to this article has been published online at https://doi.org/10.1016/j.heliyon.2022.e09065.

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